PIPERIDINYL TARGETING COMPOUNDS THAT SELECTIVELY BIND INTEGRINS

This application is a continuation in part of nonprovisional patent application serial no. 10/641,964 filed on August 15, 2003 and claims benefit of provisional patent application serial number 60/404,239, filed on 16 August 2003, which are all hereby incorporated by reference herein.

FIELD OF THE INVENTION

The current invention relates to the preparation of an affinity moiety or targeting ligand that may be used in imaging or treating integrin mediated diseases. The targeting ligand of the present invention is a member of a class of piperidinoyl carboxylic acid compounds, which possess a high binding affinity for $\alpha_V\beta_3$, $\alpha_V\beta_5$, or $\alpha_V\beta_6$ integrin receptors. The current invention also relates to targeting ligand conjugated with an imaging agent or a drug delivery vehicle such as a liposome. Also provided are targeted liposomes as drug delivery vehicle for treating cells and imaging agents for imaging cells involved in $\alpha_V\beta_3$, $\alpha_V\beta_5$, or $\alpha_V\beta_6$ -mediated disease states.

BACKGROUND OF THE INVENTION

Integrins are a family of transmembrane receptors, each of which is composed of a pair of heterodimeric, noncovalently associated glycoproteins, designated as α and β chains. The α subunit contains heavy and light chains as part of its extracellular domain, with 3-4 divalent-cation binding sites; the light chain also contains transmembrane and intracellular domains. The β-subunit contains a large extracellular domain, as well as transmembrane and intracellular domains. Integrins are cell surface receptors, which bind to extracellular matrix adhesive proteins such as fibrinogen, fibronectin, vitronectin and osteopontin. These transmembrane glycoproteins are classified by the β subunits. The $\beta3$ class of integrin family has received the most attention in recent drug discovery efforts (W.J. Hoekstra, *Current Medicinal Chemistry*,

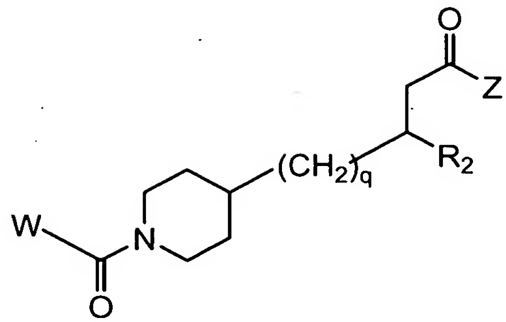
1998, 5, 195), however, the β5 class has also become a focus of attention. Some of the disease states that have been associated with a strong β3 and β5 integrin component in their etiologies are thrombosis (integrin α2bβ3 also called GPIIb/IIIa); unstable angina (GPIIb/IIIa); restenosis (GPIIb/IIIa and integrin αvβ3); arthritis, vascular disorders or osteoporosis (αvβ3); tumor angiogenesis, multiple sclerosis, neurological disorders, asthma, vascular injury or diabetic retinopathy (αvβ3 or αvβ5) and tumor metastasis (αvβ3). See S.A. Mousa, et al., *Emerging Therapeutic Targets*, **2000**, 4(2) 148-149; and W.H. Miller, et al., *Drug Discovery Today*, **2000**, 5(9), 397-40. Antibodies and/or low-molecular weight compound antagonists of αvβ3 have shown efficacy against these respective disease states in animal models (J. Samanen, *Current Pharmaceutical Design*, **1997**, 3 545-584) and thereby offer promise as therapeutic agents. Several patents have described compounds that could interact with these integrins. For example, United States Patents 5,919,792 B1, 6,211,191 B1, and WO 01/96334 and WO 01/23376 describe αvβ3 and αvβ5 integrin receptor antagonists.

The present invention provides a new class of piperidinyl compounds, which selective bind to β3, β5 or dual integrin receptors (e.g. αvβ3 and αvβ5) for the treatment of a wide variety of integrin mediated disease states.

The present invention describes the synthesis and use of piperidinoyl carboxylic acid integrin antagonists affinity moieties that may serve as a targeting agent for imaging agents or serve to direct the liposomes containing therapeutic agents to cells that express $\alpha_V\beta_3$, $\alpha_V\beta_5$, or $\alpha_V\beta_6$ integrin receptors. The liposome may carry a number of therapeutic agents, including but not limited to, steroids, immunosuppressants, antihistamines, non-steroidal anti-asthamtics, non-steroidal anti-inflammatory agents, cyclooxygenase-2 inhibitors, cytotoxic agents, gene therapy agents, radiotherapy agents, imaging agents.

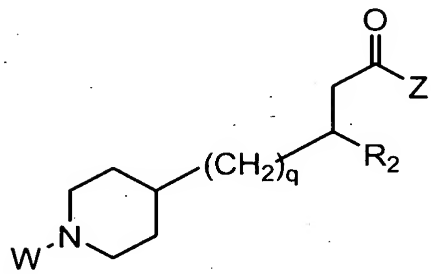
SUMMARY OF THE INVENTION

The present invention is directed to piperidinyl compounds of Formula (I):



Formula (I)

and Formula (II)



Formula (II)

wherein

W is selected from the group consisting of $-C_{0-6}alkyl(R_1)$, $-C_{1-6}alkyl(R_{1a})$, $-C_{0-6}alkyl-aryl(R_1,R_8)$, $-C_{0-6}alkyl-heterocyclyl(R_1,R_8)$, $-C_{0-6}alkoxy(R_1)$, $-C_{0-6}alkoxy-aryl(R_1,R_8)$, and $-C_{0-6}alkoxy-heterocyclyl(R_1,R_8)$,

R_1 is selected from the group consisting of hydrogen, $-N(R_4)_2$, $-N(R_4)(R_5)$, $-N(R_4)(R_6)$, $-heterocyclyl(R_8)$ and $-heteroaryl(R_8)$;

R_{1a} is selected from the group consisting of $-C(R_4)(=N-R_4)$, $-C(=N-R_4)-N(R_4)_2$, $-C(=N-R_4)-N(R_4)(R_6)$, $-C(=N-R_4)-N(R_4)-C(=O)-R_4$, $-C(=N-R_4)-N(R_4)-C(=O)-N(R_4)_2$, $-C(=N-R_4)-N(R_4)-CO_2-R_4$, $-C(=N-R_4)-N(R_4)-SO_2-C_{1-8}alkyl(R_7)$ and $-C(=N-R_4)-N(R_4)-SO_2-N(R_4)_2$;

R_4 is selected from the group consisting of hydrogen and $-C_{1-8}alkyl(R_7)$;

R_5 is selected from the group consisting of $-C(=O)-R_4$, $-C(=O)-N(R_4)_2$, $-C(=O)-cycloalkyl(R_8)$, $-C(=O)-heterocyclyl(R_8)$, $-C(=O)-aryl(R_8)$,

-C(=O)-heteroaryl(R_8), -C(=O)-N(R_4)-cycloalkyl(R_8), -C(=O)-N(R_4)-aryl(R_8), -CO_2-R_4, -CO_2-cycloalkyl(R_8), -CO_2-aryl(R_8), -C(R_4)(=N-R_4), -C(=N-R_4)-N(R_4)$_2$, -C(=N-R_4)-N(R_4)(R_6), -C(=N-R_4)-N(R_4)-C(=O)-R_4, -C(=N-R_4)-N(R_4)-C(=O)-N(R_4)$_2$, -C(=N-R_4)-N(R_4)-CO_2-R_4, -C(=N-R_4)-N(R_4)-SO_2-C_{1-8}alkyl(R_7), -C(=N-R_4)-N(R_4)-SO_2-N(R_4)$_2$, -N(R_4)-C(R_4)(=N-R_4), -N(R_4)-C(=N-R_4)-N(R_4)$_2$, -N(R_4)-C(=N-R_4)-N(R_4)(R_6), -N(R_4)-C(=N-R_4)-N(R_4)-C(=O)-R_4, -N(R_4)-C(=N-R_4)-N(R_4)-C(=O)-N(R_4)$_2$, -N(R_4)-C(=N-R_4)-N(R_4)-CO_2-R_4, -N(R_4)-C(=N-R_4)-N(R_4)-SO_2-C_{1-8}alkyl(R_7), -N(R_4)-C(=N-R_4)-N(R_4)-SO_2-N(R_4)$_2$, -SO_2-C_{1-8}alkyl(R_7), -SO_2-N(R_4)$_2$, -SO_2-cycloalkyl(R_8) and -SO_2-aryl(R_8);

R_6 is selected from the group consisting of -cycloalkyl(R_8), -heterocyclyl(R_8), -aryl(R_8) and -heteroaryl(R_8);

R_7 is one to two substituents independently selected from the group consisting of hydrogen, -C_{1-8}alkoxy(R_9), -NH_2, -NH-C_{1-8}alkyl(R_9), -N(C_{1-8}alkyl(R_9))$_2$, -C(=O)H, -C(=O)-C_{1-8}alkyl(R_9), -C(=O)-NH_2, -C(=O)-NH-C_{1-8}alkyl(R_9), -C(=O)-N(C_{1-8}alkyl(R_9))$_2$, -C(=O)-NH-aryl(R_{10}), -C(=O)-cycloalkyl(R_{10}), -C(=O)-heterocyclyl(R_{10}), -C(=O)-aryl(R_{10}), -C(=O)-heteroaryl(R_{10}), -CO_2H, -CO_2-C_{1-8}alkyl(R_9), -CO_2-aryl(R_{10}), -C(=NH)-NH_2, -SH, -S-C_{1-8}alkyl(R_9), -S-C_{1-8}alkyl-S-C_{1-8}alkyl(R_9), -S-C_{1-8}alkyl-C_{1-8}alkoxy(R_9), -S-C_{1-8}alkyl-NH-C_{1-8}alkyl(R_9), -SO_2-C_{1-8}alkyl(R_9), -SO_2-NH_2, -SO_2-NH-C_{1-8}alkyl(R_9), -SO_2-N(C_{1-8}alkyl(R_9))$_2$, -SO_2-aryl(R_{10}), cyano, (halo)$_{1-3}$, hydroxy, nitro, oxo, -cycloalkyl(R_{10}), -heterocyclyl(R_{10}), -aryl(R_{10}) and -heteroaryl(R_{10});

R_8 is one to four substituents independently selected from the group consisting of hydrogen, -C_{1-8}alkyl(R_9), -C(=O)H, -C(=O)-C_{1-8}alkyl(R_9), -C(=O)-NH_2, -C(=O)-NH-C_{1-8}alkyl(R_9), -C(=O)-N(C_{1-8}alkyl(R_9))$_2$, -C(=O)-NH-aryl(R_{10}), -C(=O)-cycloalkyl(R_{10}), -C(=O)-heterocyclyl(R_{10}), -C(=O)-aryl(R_{10}), -C(=O)-heteroaryl(R_{10}), -CO_2H, -CO_2-C_{1-8}alkyl(R_9), -CO_2-aryl(R_{10}), -C(=NH)-NH_2, -SO_2-C_{1-8}alkyl(R_9), -SO_2-NH_2, -SO_2-NH-C_{1-8}alkyl(R_9), -SO_2-N(C_{1-8}alkyl(R_9))$_2$,

$-SO_2$-aryl(R_{10}), -cycloalkyl(R_{10}) and -aryl(R_{10}) when attached to a nitrogen atom; and, wherein R_8 is one to four substituents independently selected from the group consisting of hydrogen, $-C_{1-8}$alkyl(R_9), $-C_{1-8}$alkoxy(R_9), -O-cycloalkyl(R_{10}), -O-aryl(R_{10}), -C(=O)H, -C(=O)-C_{1-8}alkyl(R_9), -C(=O)-NH_2, -C(=O)-NH-C_{1-8}alkyl(R_9), -C(=O)-N(C_{1-8}alkyl(R_9))$_2$, -C(=O)-NH-aryl(R_{10}), -C(=O)-cycloalkyl(R_{10}), -C(=O)-heterocyclyl(R_{10}), -C(=O)-aryl(R_{10}), -C(=O)-heteroaryl(R_{10}), $-CO_2H$, $-CO_2$-C_{1-8}alkyl(R_9), $-CO_2$-aryl(R_{10}), -C(=NH)-NH_2, $-SO_2$-C_{1-8}alkyl(R_9), $-SO_2$-NH_2, $-SO_2$-NH-C_{1-8}alkyl(R_9), $-SO_2$-N(C_{1-8}alkyl(R_9))$_2$, $-SO_2$-aryl(R_{10}), -SH, -S-C_{1-8}alkyl(R_9), -S-C_{1-8}alkyl-S-C_{1-8}alkyl(R_9), -S-C_{1-8}alkyl-C_{1-8}alkoxy(R_9), -S-C_{1-8}alkyl-NH-C_{1-8}alkyl(R_9), $-NH_2$, -NH-C_{1-8}alkyl(R_9), -N(C_{1-8}alkyl(R_9))$_2$, cyano, halo, hydroxy, nitro, oxo, -cycloalkyl(R_{10}), -heterocyclyl(R_{10}), -aryl(R_{10}) and -heteroaryl(R_{10}) when attached to a carbon atom;

R_9 is selected from the group consisting of hydrogen, $-C_{1-8}$alkoxy, $-NH_2$, -NH-C_{1-8}alkyl, -N(C_{1-8}alkyl)$_2$, -C(=O)H, -C(=O)-NH_2, -C(=O)-NH-C_{1-8}alkyl, -C(=O)-N(C_{1-8}alkyl)$_2$, $-CO_2H$, $-CO_2$-C_{1-8}alkyl, $-SO_2$-C_{1-8}alkyl, $-SO_2$-NH_2, $-SO_2$-NH-C_{1-8}alkyl, $-SO_2$-N(C_{1-8}alkyl)$_2$, cyano, (halo)$_{1-3}$, hydroxy, nitro and oxo;

R_{10} is one to four substituents independently selected from from the group consisting of hydrogen, $-C_{1-8}$alkyl, -C(=O)H, -C(=O)-C_{1-8}alkyl, -C(=O)-NH_2, -C(=O)-NH-C_{1-8}alkyl, -C(=O)-N(C_{1-8}alkyl)$_2$, $-CO_2H$, $-CO_2$- C_{1-4}alkyl, $-SO_2$-C_{1-8}alkyl, $-SO_2$-NH_2, $-SO_2$-NH-C_{1-8}alkyl and $-SO_2$-N(C_{1-8}alkyl)$_2$ when attached to a nitrogen atom; and, wherein R_{10} is one to four substituents independently selected from the group consisting of hydrogen, $-C_{1-8}$alkyl, $-C_{1-8}$alkoxy, -C(=O)H, -C(=O)-C_{1-8}alkyl, -C(=O)-NH_2, -C(=O)-NH-C_{1-8}alkyl, -C(=O)-N(C_{1-8}alkyl)$_2$, $-CO_2H$, $-CO_2$- C_{1-4}alkyl, $-SO_2$-C_{1-8}alkyl, $-SO_2$-NH_2, $-SO_2$-NH-C_{1-8}alkyl, $-SO_2$-N(C_{1-8}alkyl)$_2$, $-NH_2$, -NH-C_{1-8}alkyl, -N(C_{1-8}alkyl)$_2$, cyano, halo, hydroxy, nitro and oxo when attached to a carbon atom;

R_2 is selected from the group consisting of hydrogen, $-C_{1-8}$alkyl(R_7), $-C_{2-8}$alkenyl(R_7), $-C_{2-8}$alkynyl(R_7), -cycloalkyl(R_8), -heterocyclyl(R_8), -aryl(R_8) and -heteroaryl(R_8);

q is 0, 1, 2 or 3;

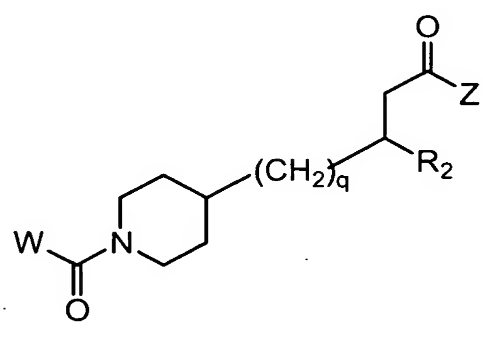
Z is selected from the group consisting of hydroxy, $-NH_2$, $-NH-C_{1-8}$alkyl, $-N(C_{1-8}alkyl)_2$, $-O-C_{1-8}$alkyl, $-O-C_{1-8}$alkyl-OH, $-O-C_{1-8}$alkylC_{1-8}alkoxy, $-O-C_{1-8}$alkylcarbonylC_{1-8}alkyl, $-O-C_{1-8}$alkyl-CO_2H, $-O-C_{1-8}$alkyl-C(O)O-C_{1-8}alkyl, $-O-C_{1-8}$alkyl-O-C(O)C_{1-8}alkyl, $-O-C_{1-8}$alkyl-NH_2, $-O-C_{1-8}$alkyl-NH-C_{1-8}alkyl, $-O-C_{1-8}$alkyl-$N(C_{1-8}alkyl)_2$, $-O-C_{1-8}$alkylamide, $-O-C_{1-8}$alkyl-C(O)-NH-C_{1-8}alkyl, $-O-C_{1-8}$alkyl-C(O)-$N(C_{1-8}alkyl)_2$ and –NHC(O)C_{1-8}alkyl.

and pharmaceutically acceptable salts, racemic mixtures and enantiomers thereof.

The present invention is also directed to methods for producing the instant piperidinyl compounds and pharmaceutical compositions and medicaments thereof.

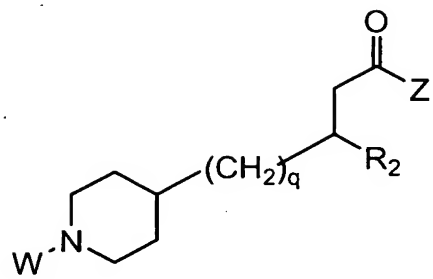
The present invention is further directed to a method for treating or ameliorating an integrin receptor mediated disorder.

In one embodiment of the present invention comprise targeting ligands of Formula (I):



Formula (I)

and Formula (II):



Formula (II)

wherein

W is selected from the group consisting of -$C_{0\text{-}6}$alkyl(R_1), -$C_{1\text{-}6}$alkyl(R_{1a}), -$C_{0\text{-}6}$alkyl-aryl(R_1,R_8), -$C_{0\text{-}6}$alkyl-heterocyclyl(R_1,R_8), -$C_{0\text{-}6}$alkoxy(R_1), -$C_{0\text{-}6}$alkoxy-aryl(R_1,R_8), and -$C_{0\text{-}6}$alkoxy-heterocyclyl(R_1,R_8);

R_1 is selected from the group consisting of hydrogen, -N(R_4)$_2$, -N(R_4)(R_5), -N(R_4)(R_6), -heterocyclyl(R_8) and -heteroaryl(R_8);

R_{1a} is selected from the group consisting of -C(R_4)(=N-R_4), -C(=N-R_4)-N(R_4)$_2$, -C(=N-R_4)-N(R_4)(R_6), -C(=N-R_4)-N(R_4)-C(=O)-R_4, -C(=N-R_4)-N(R_4)-C(=O)-N(R_4)$_2$, -C(=N-R_4)-N(R_4)-CO_2-R_4, -C(=N-R_4)-N(R_4)-SO_2-$C_{1\text{-}8}$alkyl(R_7) and -C(=N-R_4)-N(R_4)-SO_2-N(R_4)$_2$;

R_4 is selected from the group consisting of hydrogen and -$C_{1\text{-}8}$alkyl(R_7);

R_5 is selected from the group consisting of -C(=O)-R_4, -C(=O)-N(R_4)$_2$, -C(=O)-cycloalkyl(R_8), -C(=O)-heterocyclyl(R_8), -C(=O)-aryl(R_8), -C(=O)-heteroaryl(R_8), -C(=O)-N(R_4)-cycloalkyl(R_8), -C(=O)-N(R_4)-aryl(R_8), -CO_2-R_4, -CO_2-cycloalkyl(R_8), -CO_2-aryl(R_8), -C(R_4)(=N-R_4), -C(=N-R_4)-N(R_4)$_2$, -C(=N-R_4)-N(R_4)(R_6), -C(=N-R_4)-N(R_4)-C(=O)-R_4, -C(=N-R_4)-N(R_4)-C(=O)-N(R_4)$_2$, -C(=N-R_4)-N(R_4)-CO_2-R_4, -C(=N-R_4)-N(R_4)-SO_2-$C_{1\text{-}8}$alkyl(R_7), -C(=N-R_4)-N(R_4)-SO_2-N(R_4)$_2$, -N(R_4)-C(R_4)(=N-R_4), -N(R_4)-C(=N-R_4)-N(R_4)$_2$, -N(R_4)-C(=N-R_4)-N(R_4)(R_6), -N(R_4)-C(=N-R_4)-N(R_4)-C(=O)-R_4, -N(R_4)-C(=N-R_4)-N(R_4)-C(=O)-N(R_4)$_2$, -N(R_4)-C(=N-R_4)-N(R_4)-CO_2-R_4, -N(R_4)-C(=N-R_4)-N(R_4)-SO_2-$C_{1\text{-}8}$alkyl(R_7), -N(R_4)-C(=N-R_4)-N(R_4)-SO_2-N(R_4)$_2$, -SO_2-$C_{1\text{-}8}$alkyl(R_7), -SO_2-N(R_4)$_2$,

$-SO_2$-cycloalkyl(R_8) and $-SO_2$-aryl(R_8);

R_6 is selected from the group consisting of -cycloalkyl(R_8), -heterocyclyl(R_8), -aryl(R_8) and -heteroaryl(R_8);

R_7 is one to two substituents independently selected from the group consisting of hydrogen, $-C_{1-8}$alkoxy(R_9), $-NH_2$, $-NH-C_{1-8}$alkyl(R_9), $-N(C_{1-8}$alkyl$(R_9))_2$, -C(=O)H, $-C(=O)-C_{1-8}$alkyl(R_9), $-C(=O)-NH_2$, $-C(=O)-NH-C_{1-8}$alkyl(R_9), $-C(=O)-N(C_{1-8}$alkyl$(R_9))_2$, -C(=O)-NH-aryl(R_{10}), -C(=O)-cycloalkyl(R_{10}), -C(=O)-heterocyclyl(R_{10}), -C(=O)-aryl(R_{10}), -C(=O)-heteroaryl(R_{10}), $-CO_2H$, $-CO_2-C_{1-8}$alkyl(R_9), $-CO_2$-aryl(R_{10}), $-C(=NH)-NH_2$, -SH, $-S-C_{1-8}$alkyl(R_9), $-S-C_{1-8}$alkyl$-S-C_{1-8}$alkyl(R_9), $-S-C_{1-8}$alkyl$-C_{1-8}$alkoxy(R_9), $-S-C_{1-8}$alkyl$-NH-C_{1-8}$alkyl(R_9), $-SO_2-C_{1-8}$alkyl(R_9), $-SO_2-NH_2$, $-SO_2-NH-C_{1-8}$alkyl(R_9), $-SO_2-N(C_{1-8}$alkyl$(R_9))_2$, $-SO_2$-aryl(R_{10}), cyano, $(\text{halo})_{1-3}$, hydroxy, nitro, oxo, -cycloalkyl(R_{10}), -heterocyclyl(R_{10}), -aryl(R_{10}) and -heteroaryl(R_{10});

R_8 is one to four substituents independently selected from the group consisting of hydrogen, $-C_{1-8}$alkyl(R_9), -C(=O)H, $-C(=O)-C_{1-8}$alkyl(R_9), $-C(=O)-NH_2$, $-C(=O)-NH-C_{1-8}$alkyl(R_9), $-C(=O)-N(C_{1-8}$alkyl$(R_9))_2$, -C(=O)-NH-aryl(R_{10}), -C(=O)-cycloalkyl(R_{10}), -C(=O)-heterocyclyl(R_{10}), -C(=O)-aryl(R_{10}), -C(=O)-heteroaryl(R_{10}), $-CO_2H$, $-CO_2-C_{1-8}$alkyl(R_9), $-CO_2$-aryl(R_{10}), $-C(=NH)-NH_2$, $-SO_2-C_{1-8}$alkyl(R_9), $-SO_2-NH_2$, $-SO_2-NH-C_{1-8}$alkyl(R_9), $-SO_2-N(C_{1-8}$alkyl$(R_9))_2$, $-SO_2$-aryl(R_{10}), -cycloalkyl(R_{10}) and -aryl(R_{10}) when attached to a nitrogen atom; and, wherein R_8 is one to four substituents independently selected from the group consisting of hydrogen, $-C_{1-8}$alkyl(R_9), $-C_{1-8}$alkoxy(R_9), -O-cycloalkyl(R_{10}), -O-aryl(R_{10}), -C(=O)H, $-C(=O)-C_{1-8}$alkyl(R_9), $-NHC(=O)-C_{1-8}$alkyl(R_9), $-C(=O)-NH_2$, $-C(=O)-NH-C_{1-8}$alkyl(R_9), $-C(=O)-N(C_{1-8}$alkyl$(R_9))_2$, -C(=O)-NH-aryl(R_{10}), $-NHC(=O)-NH_2$, $-NHC(=O)-NH-C_{1-8}$alkyl(R_9), $-NHC(=O)-N(C_{1-8}$alkyl$(R_9))_2$, -NHC(=O)-NH-aryl(R_{10}), $-NHC(=O)-O-C_{1-8}$alkyl(R_9), -NHC(=O)-O-aryl(R_{10}), -C(=O)-cycloalkyl(R_{10}), -C(=O)-heterocyclyl(R_{10}), -C(=O)-aryl(R_{10}), -C(=O)-heteroaryl(R_{10}),

$-NHC(=O)$-cycloalkyl(R_{10}), $-NHC(=O)$-heterocyclyl(R_{10}), $-NHC(=O)$-aryl(R_{10}), $-NHC(=O)$-heteroaryl(R_{10}), $-CO_2H$, $-CO_2$-C_{1-8}alkyl(R_9), $-CO_2$-aryl(R_{10}), $-C(=NH)-NH_2$, $-SO_2$-C_{1-8}alkyl(R_9), $-SO_2-NH_2$, $-SO_2$-NH-C_{1-8}alkyl(R_9), $-SO_2$-N(C_{1-8}alkyl(R_9))$_2$, $-SO_2$-aryl(R_{10}), $-NHSO_2$-C_{1-8}alkyl(R_9), $-NHSO_2$-aryl(R_{10}), -SH, -S-C_{1-8}alkyl(R_9), -S-C_{1-8}alkyl-S-C_{1-8}alkyl(R_9), -S-C_{1-8}alkyl-C_{1-8}alkoxy(R_9), -S-C_{1-8}alkyl-NH-C_{1-8}alkyl(R_9), $-NH_2$, -NH-C_{1-8}alkyl(R_9), -N(C_{1-8}alkyl(R_9))$_2$, cyano, halo, hydroxy, nitro, oxo, -cycloalkyl(R_{10}), -heterocyclyl(R_{10}), -aryl(R_{10}), and -heteroaryl(R_{10}) when attached to a carbon atom;

R_9 is selected from the group consisting of hydrogen, -C_{1-8}alkoxy, $-NH_2$, -NH-C_{1-8}alkyl, -N(C_{1-8}alkyl)$_2$, $-C(=O)H$, $-C(=O)-NH_2$, $-C(=O)$-NH-C_{1-8}alkyl, $-C(=O)$-N(C_{1-8}alkyl)$_2$, $-CO_2H$, $-CO_2$-C_{1-8}alkyl, $-SO_2$-C_{1-8}alkyl, $-SO_2-NH_2$, $-SO_2$-NH-C_{1-8}alkyl, $-SO_2$-N(C_{1-8}alkyl)$_2$, cyano, (halo)$_{1-3}$, hydroxy, nitro and oxo;

R_{10} is one to four substituents independently selected from the group consisting of hydrogen, -C_{1-8}alkyl, $-C(=O)H$, $-C(=O)$-C_{1-8}alkyl, $-C(=O)-NH_2$, $-C(=O)$-NH-C_{1-8}alkyl, $-C(=O)$-N(C_{1-8}alkyl)$_2$, $-CO_2H$, $-CO_2$- C_{1-4}alkyl, $-SO_2$-C_{1-8}alkyl, $-SO_2-NH_2$, $-SO_2$-NH-C_{1-8}alkyl and $-SO_2$-N(C_{1-8}alkyl)$_2$ when attached to a nitrogen atom; and, wherein R_{10} is one to four substituents independently selected from the group consisting of hydrogen, -C_{1-8}alkyl, -C_{1-8}alkoxy, $-C(=O)H$, $-C(=O)$-C_{1-8}alkyl, $-C(=O)-NH_2$, $-C(=O)$-NH-C_{1-8}alkyl, $-C(=O)$-N(C_{1-8}alkyl)$_2$, $-CO_2H$, $-CO_2$- C_{1-4}alkyl, $-SO_2$-C_{1-8}alkyl, $-SO_2-NH_2$, $-SO_2$-NH-C_{1-8}alkyl, $-SO_2$-N(C_{1-8}alkyl)$_2$, $-NH_2$, -NH-C_{1-8}alkyl, -N(C_{1-8}alkyl)$_2$, cyano, halo, hydroxy, nitro and oxo when attached to a carbon atom;

q is 0, 1, 2, or 3;

R_{2a} is selected from the group consisting of -C_{1-8}alkyl(R_7)(R_{11}), -C_{2-8}alkenyl(R_7)(R_{11}), -C_{2-8}alkynyl(R_7)(R_{11}), -cycloalkyl(R_7)(R_{11}), -heterocyclyl(R_8)(R_{12}), -aryl(R_8)(R_{12}) and -heteroaryl(R_8)(R_{12});

R_{11} is selected from the group consisting of -C_{1-8}alkyl(R_{14}),

-O-C_{1-8}alkyl(R_{14}), -NH-C_{1-8}alkyl(R_{14}), -S-C_{1-8}alkyl(R_{14}), -C(=O)C_{1-8}alkyl(R_{14}), -O-C(=O)C_{1-8}alkyl(R_{14}), -NH-C(=O)C_{1-8}alkyl(R_{14}), -C(=O)OC_{1-8}alkyl(R_{14}), -C(=O)NHC_{1-8}alkyl(R_{14}), -O-C(=O)OC_{1-8}alkyl(R_{14}), -O-C(=O)NHC_{1-8}alkyl(R_{14}), -NH-C(=O)OC_{1-8}alkyl(R_{14}), -NH-C(=O)NHC_{1-8}alkyl(R_{14}), -C(=O)C_{1-8}alkylC(=O)(R_{14}), -O-C(=O)C_{1-8}alkylC(=O)(R_{14}), -NH-C(=O)C_{1-8}alkylC(=O)(R_{14}), -C(=O)OC_{1-8}alkylC(=O)(R_{14}), -O-C(=O)OC_{1-8}alkylC(=O)(R_{14}), -NH-C(=O)OC_{1-8}alkylC(=O)(R_{14}), -C(=O)NHC_{1-8}alkylC(=O)(R_{14}), -O-C(=O)NHC_{1-8}alkylC(=O)(R_{14}), -NH-C(=O)NHC_{1-8}alkylC(=O)(R_{14}), -$OCH_2CH_2O(CH_2CH_2O)_rCH_2CH_2$($R_{14}$), -$NHCH_2CH_2O(CH_2CH_2O)_rCH_2CH_2$($R_{14}$), -$SCH_2CH_2O(CH_2CH_2O)_rCH_2CH_2$($R_{14}$), -$OCH_2CH_2O(CH_2CH_2O)_rCH_2$C(=O)($R_{14}$), -$NHCH_2CH_2O(CH_2CH_2O)_rCH_2$C(=O)($R_{14}$), -$SCH_2CH_2O(CH_2CH_2O)_rCH_2$C(=O)($R_{14}$), -OC(=O)$CH_2O(CH_2CH_2O)_rCH_2CH_2$($R_{14}$), -OC(=O)$OCH_2CH_2O(CH_2CH_2O)_rCH_2CH_2$($R_{14}$), -OC(=O)$NHCH_2CH_2O(CH_2CH_2O)_rCH_2CH_2$($R_{14}$), -NH(C=O)$CH_2O(CH_2CH_2O)_rCH_2CH_2$($R_{14}$), -NHC(=O)$OCH_2CH_2O(CH_2CH_2O)_rCH_2CH_2$($R_{14}$), -NHC(=O)$NHCH_2CH_2O(CH_2CH_2O)_rCH_2CH_2$($R_{14}$), -$SO_2CH_2CH_2O(CH_2CH_2O)_rCH_2CH_2$($R_{14}$), -$SO_2NHCH_2CH_2O(CH_2CH_2O)_rCH_2CH_2$($R_{14}$), -C(=O)$CH_2O(CH_2CH_2O)_rCH_2$C(=O)($R_{14}$), -OC(=O)$CH_2O(CH_2CH_2O)_rCH_2$C(=O)($R_{14}$), -OC(=O)$OCH_2CH_2O(CH_2CH_2O)_rCH_2$C(=O)($R_{14}$), -OC(=O)$NHCH_2CH_2O(CH_2CH_2O)_rCH_2$C(=O)($R_{14}$), -NH(C=O)$CH_2O(CH_2CH_2O)_rCH_2$C(=O)($R_{14}$), -NHC(=O)$OCH_2CH_2O(CH_2CH_2O)_rCH_2$C(=O)($R_{14}$), -NHC(=O)$NHCH_2CH_2O(CH_2CH_2O)_rCH_2$C(=O)($R_{14}$), -$SO_2CH_2CH_2O(CH_2CH_2O)_rCH_2$C(=O)($R_{14}$), and -$SO_2NHCH_2CH_2O(CH_2CH_2O)_rCH_2$C(=O)($R_{14}$);

R_{12} is selected from the group consisting of $-C_{1-8}alkyl(R_{14})$, $-O-C_{1-8}alkyl(R_{14})$, $-NH-C_{1-8}alkyl(R_{14})$, $-S-C_{1-8}alkyl(R_{14})$, $-CH_2O-C_{1-8}alkyl(R_{14})$, $-CH_2NH-C_{1-8}alkyl(R_{14})$, $-CH_2S-C_{1-8}alkyl(R_{14})$, $-C(=O)C_{1-8}alkyl(R_{14})$, $-O-C(=O)C_{1-8}alkyl(R_{14})$, $-NH-C(=O)C_{1-8}alkyl(R_{14})$, $-CH_2O-C(=O)C_{1-8}alkyl(R_{14})$, $-CH_2NH-C(=O)C_{1-8}alkyl(R_{14})$, $-C(=O)OC_{1-8}alkyl(R_{14})$, $-C(=O)NHC_{1-8}alkyl(R_{14})$, $-O-C(=O)OC_{1-8}alkyl(R_{14})$, $-O-C(=O)NHC_{1-8}alkyl(R_{14})$, $-NH-C(=O)OC_{1-8}alkyl(R_{14})$, $-NH-C(=O)NHC_{1-8}alkyl(R_{14})$, $-CH_2O-C(=O)OC_{1-8}alkyl(R_{14})$, $-CH_2O-C(=O)NHC_{1-8}alkyl(R_{14})$, $-CH_2NH-C(=O)OC_{1-8}alkyl(R_{14})$, $-CH_2NH-C(=O)NHC_{1-8}alkyl(R_{14})$, $-C(=O)C_{1-8}alkylC(=O)(R_{14})$, $-O-C(=O)C_{1-8}alkylC(=O)(R_{14})$, $-NH-C(=O)C_{1-8}alkylC(=O)(R_{14})$, $-CH_2O-C(=O)C_{1-8}alkylC(=O)(R_{14})$, $-CH_2NH-C(=O)C_{1-8}alkylC(=O)(R_{14})$, $-C(=O)OC_{1-8}alkylC(=O)(R_{14})$, $-O-C(=O)OC_{1-8}alkylC(=O)(R_{14})$, $-NH-C(=O)OC_{1-8}alkylC(=O)(R_{14})$, $-CH_2O-C(=O)OC_{1-8}alkylC(=O)(R_{14})$, $-CH_2NH-C(=O)OC_{1-8}alkylC(=O)(R_{14})$, $-C(=O)NHC_{1-8}alkylC(=O)(R_{14})$, $-O-C(=O)NHC_{1-8}alkylC(=O)(R_{14})$, $-NH-C(=O)NHC_{1-8}alkylC(=O)(R_{14})$, $-CH_2O-C(=O)NHC_{1-8}alkylC(=O)(R_{14})$, $-CH_2NH-C(=O)NHC_{1-8}alkylC(=O)(R_{14})$, $-OCH_2CH_2O(CH_2CH_2O)_rCH_2CH_2(R_{14})$, $-NHCH_2CH_2O(CH_2CH_2O)_rCH_2CH_2(R_{14})$, $-SCH_2CH_2O(CH_2CH_2O)_rCH_2CH_2(R_{14})$, $-OCH_2CH_2O(CH_2CH_2O)_rCH_2C(=O)(R_{14})$, $-NHCH_2CH_2O(CH_2CH_2O)_rCH_2C(=O)(R_{14})$, $-SCH_2CH_2O(CH_2CH_2O)_rCH_2C(=O)(R_{14})$, $-OC(=O)CH_2O(CH_2CH_2O)_rCH_2CH_2(R_{14})$, $-OC(=O)OCH_2CH_2O(CH_2CH_2O)_rCH_2CH_2(R_{14})$, $-OC(=O)NHCH_2CH_2O(CH_2CH_2O)_rCH_2CH_2(R_{14})$, $-NH(C=O)CH_2O(CH_2CH_2O)_rCH_2CH_2(R_{14})$, $-NHC(=O)OCH_2CH_2O(CH_2CH_2O)_rCH_2CH_2(R_{14})$, $-NHC(=O)NHCH_2CH_2O(CH_2CH_2O)_rCH_2CH_2(R_{14})$, $-SO_2CH_2CH_2O(CH_2CH_2O)_rCH_2CH_2(R_{14})$,

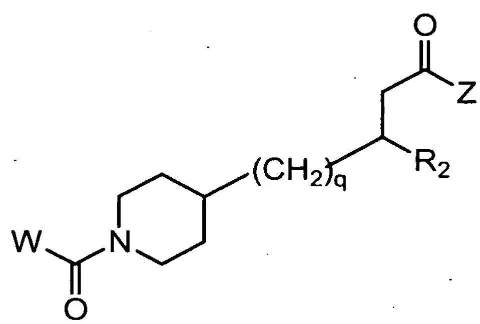
$-SO_2NHCH_2CH_2O(CH_2CH_2O)_rCH_2CH_2(R_{14})$,
$-CH_2OCH_2CH_2O(CH_2CH_2O)_rCH_2CH_2(R_{14})$,
$-CH_2NHCH_2CH_2O(CH_2CH_2O)_rCH_2CH_2(R_{14})$,
$-CH_2SCH_2CH_2O(CH_2CH_2O)_rCH_2CH_2(R_{14})$,
$-CH_2OCH_2CH_2O(CH_2CH_2O)_rCH_2C(=O)(R_{14})$,
$-CH_2NHCH_2CH_2O(CH_2CH_2O)_rCH_2C(=O)(R_{14})$,
$-CH_2SCH_2CH_2O(CH_2CH_2O)_rCH_2C(=O)(R_{14})$,
$-CH_2OC(=O)CH_2O(CH_2CH_2O)_rCH_2CH_2(R_{14})$,
$-CH_2OC(=O)OCH_2CH_2O(CH_2CH_2O)_rCH_2CH_2(R_{14})$,
$-CH_2OC(=O)NHCH_2CH_2O(CH_2CH_2O)_rCH_2CH_2(R_{14})$,
$-CH_2NH(C=O)CH_2O(CH_2CH_2O)_rCH_2CH_2(R_{14})$,
$-CH_2NHC(=O)OCH_2CH_2O(CH_2CH_2O)_rCH_2CH_2(R_{14})$,
$-CH_2NHC(=O)NHCH_2CH_2O(CH_2CH_2O)_rCH_2CH_2(R_{14})$,
$-C(=O)CH_2O(CH_2CH_2O)_rCH_2C(=O)(R_{14})$,
$-OC(=O)CH_2O(CH_2CH_2O)_rCH_2C(=O)(R_{14})$,
$-OC(=O)OCH_2CH_2O(CH_2CH_2O)_rCH_2C(=O)(R_{14})$,
$-OC(=O)NHCH_2CH_2O(CH_2CH_2O)_rCH_2C(=O)(R_{14})$,
$-NH(C=O)CH_2O(CH_2CH_2O)_rCH_2C(=O)(R_{14})$,
$-NHC(=O)OCH_2CH_2O(CH_2CH_2O)_rCH_2C(=O)(R_{14})$,
$-NHC(=O)NHCH_2CH_2O(CH_2CH_2O)_rCH_2C(=O)(R_{14})$,
$-SO_2CH_2CH_2O(CH_2CH_2O)_rCH_2C(=O)(R_{14})$,
$-SO_2NHCH_2CH_2O(CH_2CH_2O)_rCH_2C(=O)(R_{14})$,
$-CH_2OC(=O)CH_2O(CH_2CH_2O)_rCH_2C(=O)(R_{14})$,
$-CH_2OC(=O)OCH_2CH_2O(CH_2CH_2O)_rCH_2C(=O)(R_{14})$,
$-CH_2OC(=O)NHCH_2CH_2O(CH_2CH_2O)_rCH_2C(=O)(R_{14})$,
$-CH_2NH(C=O)CH_2O(CH_2CH_2O)_rCH_2C(=O)(R_{14})$,
$-CH_2NHC(=O)OCH_2CH_2O(CH_2CH_2O)_rCH_2C(=O)(R_{14})$, and
$-CH_2NHC(=O)NHCH_2CH_2O(CH_2CH_2O)_rCH_2C(=O)(R_{14})$;

$R_{14}$when R_{11} and R_{12} terminates with a C(=O)is selected from the group consisting of hydrogen, OH, , $-OC_{1-4}$alkyl and NH_2; otherwise $R_{14}$is selected from the group consisting of -OH, -SH, COOH, and $-COOC_{1-4}$alkyl;

Z is selected from the group consisting of hydroxy, $-NH_2$, $-NH-C_{1-8}$alkyl, $-N(C_{1-8}alkyl)_2$, $-O-C_{1-8}$alkyl, $-O-C_{1-8}$alkyl-OH, $-O-C_{1-8}$alkylC_{1-8}alkoxy, $-O-C_{1-8}$alkylcarbonylC_{1-8}alkyl, $-O-C_{1-8}$alkyl-CO_2H, $-O-C_{1-8}$alkyl-C(O)O-C_{1-8}alkyl, $-O-C_{1-8}$alkyl-O-C(O)C_{1-8}alkyl, $-O-C_{1-8}$alkyl-NH_2, $-O-C_{1-8}$alkyl-NH-C_{1-8}alkyl, $-O-C_{1-8}$alkyl-N(C_{1-8}alkyl$)_2$, $-O-C_{1-8}$alkylamide, $-O-C_{1-8}$alkyl-C(O)-NH-C_{1-8}alkyl, $-O-C_{1-8}$alkyl-C(O)-N(C_{1-8}alkyl$)_2$ and –NHC(O)C_{1-8}alkyl;

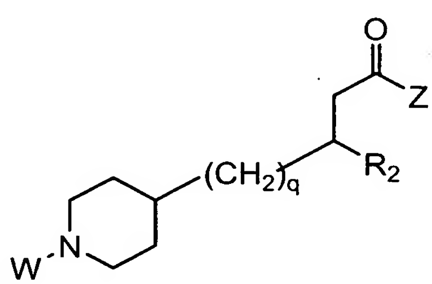
and pharmaceutically acceptable salts, racemic mixtures and enantiomers thereof.

In one embodiment of the present invention comprises a targeting conjugate of Formula (I):



Formula (I)

and Formula (II):



Formula (II)

wherein

W is selected from the group consisting of $-C_{0-6}$alkyl(R_1), $-C_{1-6}$alkyl(R_{1a}), $-C_{0-6}$alkyl-aryl(R_1,R_8), $-C_{0-6}$alkyl-heterocyclyl(R_1,R_8), $-C_{0-6}$alkoxy(R_1), $-C_{0-6}$alkoxy-aryl(R_1,R_8), and $-C_{0-6}$alkoxy-heterocyclyl(R_1,R_8);

R_1 is selected from the group consisting of hydrogen, -N(R_4)$_2$, -N(R_4)(R_5), -N(R_4)(R_6), -heterocyclyl(R_8) and -heteroaryl(R_8);

R_{1a} is selected from the group consisting of -C(R_4)(=N-R_4), -C(=N-R_4)-N(R_4)$_2$, -C(=N-R_4)-N(R_4)(R_6), -C(=N-R_4)-N(R_4)-C(=O)-R_4, -C(=N-R_4)-N(R_4)-C(=O)-N(R_4)$_2$, -C(=N-R_4)-N(R_4)-CO_2-R_4, -C(=N-R_4)-N(R_4)-SO_2-C_{1-8}alkyl(R_7) and -C(=N-R_4)-N(R_4)-SO_2-N(R_4)$_2$;

R_4 is selected from the group consisting of hydrogen and -C_{1-8}alkyl(R_7);

R_5 is selected from the group consisting of -C(=O)-R_4, -C(=O)-N(R_4)$_2$, -C(=O)-cycloalkyl(R_8), -C(=O)-heterocyclyl(R_8), -C(=O)-aryl(R_8), -C(=O)-heteroaryl(R_8), -C(=O)-N(R_4)-cycloalkyl(R_8), -C(=O)-N(R_4)-aryl(R_8), -CO_2-R_4, -CO_2-cycloalkyl(R_8), -CO_2-aryl(R_8), -C(R_4)(=N-R_4), -C(=N-R_4)-N(R_4)$_2$, -C(=N-R_4)-N(R_4)(R_6), -C(=N-R_4)-N(R_4)-C(=O)-R_4, -C(=N-R_4)-N(R_4)-C(=O)-N(R_4)$_2$, -C(=N-R_4)-N(R_4)-CO_2-R_4, -C(=N-R_4)-N(R_4)-SO_2-C_{1-8}alkyl(R_7), -C(=N-R_4)-N(R_4)-SO_2-N(R_4)$_2$, -N(R_4)-C(R_4)(=N-R_4), -N(R_4)-C(=N-R_4)-N(R_4)$_2$, -N(R_4)-C(=N-R_4)-N(R_4)(R_6), -N(R_4)-C(=N-R_4)-N(R_4)-C(=O)-R_4, -N(R_4)-C(=N-R_4)-N(R_4)-C(=O)-N(R_4)$_2$, -N(R_4)-C(=N-R_4)-N(R_4)-CO_2-R_4, -N(R_4)-C(=N-R_4)-N(R_4)-SO_2-C_{1-8}alkyl(R_7), -N(R_4)-C(=N-R_4)-N(R_4)-SO_2-N(R_4)$_2$, -SO_2-C_{1-8}alkyl(R_7), -SO_2-N(R_4)$_2$, -SO_2-cycloalkyl(R_8) and -SO_2-aryl(R_8);

R_6 is selected from the group consisting of -cycloalkyl(R_8), -heterocyclyl(R_8), -aryl(R_8) and -heteroaryl(R_8);

R_7 is one to two substituents independently selected from the group consisting of hydrogen, -C_{1-8}alkoxy(R_9), -NH_2, -NH-C_{1-8}alkyl(R_9), -N(C_{1-8}alkyl(R_9))$_2$, -C(=O)H, -C(=O)-C_{1-8}alkyl(R_9), -C(=O)-NH_2, -C(=O)-NH-C_{1-8}alkyl(R_9), -C(=O)-N(C_{1-8}alkyl(R_9))$_2$, -C(=O)-NH-aryl(R_{10}), -C(=O)-cycloalkyl(R_{10}), -C(=O)-heterocyclyl(R_{10}), -C(=O)-aryl(R_{10}), -C(=O)-heteroaryl(R_{10}), -CO_2H,

$-CO_2-C_{1-8}alkyl(R_9)$, $-CO_2-aryl(R_{10})$, $-C(=NH)-NH_2$, -SH, $-S-C_{1-8}alkyl(R_9)$, $-S-C_{1-8}alkyl-S-C_{1-8}alkyl(R_9)$, $-S-C_{1-8}alkyl-C_{1-8}alkoxy(R_9)$, $-S-C_{1-8}alkyl-NH-C_{1-8}alkyl(R_9)$, $-SO_2-C_{1-8}alkyl(R_9)$, $-SO_2-NH_2$, $-SO_2-NH-C_{1-8}alkyl(R_9)$, $-SO_2-N(C_{1-8}alkyl(R_9))_2$, $-SO_2-aryl(R_{10})$, cyano, $(halo)_{1-3}$, hydroxy, nitro, oxo, $-cycloalkyl(R_{10})$, $-heterocyclyl(R_{10})$, $-aryl(R_{10})$ and $-heteroaryl(R_{10})$;

R_8 is one to four substituents independently selected from the group consisting of hydrogen, $-C_{1-8}alkyl(R_9)$, -C(=O)H, $-C(=O)-C_{1-8}alkyl(R_9)$, $-C(=O)-NH_2$, $-C(=O)-NH-C_{1-8}alkyl(R_9)$, $-C(=O)-N(C_{1-8}alkyl(R_9))_2$, $-C(=O)-NH-aryl(R_{10})$, $-C(=O)-cycloalkyl(R_{10})$, $-C(=O)-heterocyclyl(R_{10})$, $-C(=O)-aryl(R_{10})$, $-C(=O)-heteroaryl(R_{10})$, $-CO_2H$, $-CO_2-C_{1-8}alkyl(R_9)$, $-CO_2-aryl(R_{10})$, $-C(=NH)-NH_2$, $-SO_2-C_{1-8}alkyl(R_9)$, $-SO_2-NH_2$, $-SO_2-NH-C_{1-8}alkyl(R_9)$, $-SO_2-N(C_{1-8}alkyl(R_9))_2$, $-SO_2-aryl(R_{10})$, $-cycloalkyl(R_{10})$ and $-aryl(R_{10})$ when attached to a nitrogen atom; and, wherein R_8 is one to four substituents independently selected from the group consisting of hydrogen, $-C_{1-8}alkyl(R_9)$, $-C_{1-8}alkoxy(R_9)$, $-O-cycloalkyl(R_{10})$, $-O-aryl(R_{10})$, -C(=O)H, $-C(=O)-C_{1-8}alkyl(R_9)$, $-NHC(=O)-C_{1-8}alkyl(R_9)$, $-C(=O)-NH_2$, $-C(=O)-NH-C_{1-8}alkyl(R_9)$, $-C(=O)-N(C_{1-8}alkyl(R_9))_2$, $-C(=O)-NH-aryl(R_{10})$, $-NHC(=O)-NH_2$, $-NHC(=O)-NH-C_{1-8}alkyl(R_9)$, $-NHC(=O)-N(C_{1-8}alkyl(R_9))_2$, $-NHC(=O)-NH-aryl(R_{10})$, $-NHC(=O)-O-C_{1-8}alkyl(R_9)$, $-NHC(=O)-O-aryl(R_{10})$, $-C(=O)-cycloalkyl(R_{10})$, $-C(=O)-heterocyclyl(R_{10})$, $-C(=O)-aryl(R_{10})$, $-C(=O)-heteroaryl(R_{10})$, $-NHC(=O)-cycloalkyl(R_{10})$, $-NHC(=O)-heterocyclyl(R_{10})$, $-NHC(=O)-aryl(R_{10})$, $-NHC(=O)-heteroaryl(R_{10})$, $-CO_2H$, $-CO_2-C_{1-8}alkyl(R_9)$, $-CO_2-aryl(R_{10})$, $-C(=NH)-NH_2$, $-SO_2-C_{1-8}alkyl(R_9)$, $-SO_2-NH_2$, $-SO_2-NH-C_{1-8}alkyl(R_9)$, $-SO_2-N(C_{1-8}alkyl(R_9))_2$, $-SO_2-aryl(R_{10})$, $-NHSO_2-C_{1-8}alkyl(R_9)$, $-NHSO_2-aryl(R_{10})$, -SH, $-S-C_{1-8}alkyl(R_9)$, $-S-C_{1-8}alkyl-S-C_{1-8}alkyl(R_9)$, $-S-C_{1-8}alkyl-C_{1-8}alkoxy(R_9)$, $-S-C_{1-8}alkyl-NH-C_{1-8}alkyl(R_9)$, $-NH_2$, $-NH-C_{1-8}alkyl(R_9)$, $-N(C_{1-8}alkyl(R_9))_2$, cyano, halo, hydroxy, nitro, oxo, $-cycloalkyl(R_{10})$, $-heterocyclyl(R_{10})$, $-aryl(R_{10})$, and $-heteroaryl(R_{10})$ when attached to a carbon atom;

R_9 is selected from the group consisting of hydrogen, $-C_{1-8}alkoxy$, $-NH_2$, $-NH-C_{1-8}alkyl$,

$-N(C_{1-8}alkyl)_2$, $-C(=O)H$, $-C(=O)-NH_2$, $-C(=O)-NH-C_{1-8}alkyl$, $-C(=O)-N(C_{1-8}alkyl)_2$, $-CO_2H$, $-CO_2-C_{1-8}alkyl$, $-SO_2-C_{1-8}alkyl$, $-SO_2-NH_2$, $-SO_2-NH-C_{1-8}alkyl$, $-SO_2-N(C_{1-8}alkyl)_2$, cyano, $(halo)_{1-3}$, hydroxy, nitro and oxo;

R_{10} is one to four substituents independently selected from the group consisting of hydrogen, $-C_{1-8}alkyl$, $-C(=O)H$, $-C(=O)-C_{1-8}alkyl$, $-C(=O)-NH_2$, $-C(=O)-NH-C_{1-8}alkyl$, $-C(=O)-N(C_{1-8}alkyl)_2$, $-CO_2H$, $-CO_2-C_{1-4}alkyl$, $-SO_2-C_{1-8}alkyl$, $-SO_2-NH_2$, $-SO_2-NH-C_{1-8}alkyl$ and $-SO_2-N(C_{1-8}alkyl)_2$ when attached to a nitrogen atom; and, wherein R_{10} is one to four substituents independently selected from the group consisting of hydrogen, $-C_{1-8}alkyl$, $-C_{1-8}alkoxy$, $-C(=O)H$, $-C(=O)-C_{1-8}alkyl$, $-C(=O)-NH_2$, $-C(=O)-NH-C_{1-8}alkyl$, $-C(=O)-N(C_{1-8}alkyl)_2$, $-CO_2H$, $-CO_2-C_{1-4}alkyl$, $-SO_2-C_{1-8}alkyl$, $-SO_2-NH_2$, $-SO_2-NH-C_{1-8}alkyl$, $-SO_2-N(C_{1-8}alkyl)_2$, $-NH_2$, $-NH-C_{1-8}alkyl$, $-N(C_{1-8}alkyl)_2$, cyano, halo, hydroxy, nitro and oxo when attached to a carbon atom;

q is 0, 1, 2, or 3;

R_{2a} is selected from the group consisting of $-C_{1-8}alkyl(R_7)(R_{11})$, $-C_{2-8}alkenyl(R_7)(R_{11})$, $-C_{2-8}alkynyl(R_7)(R_{11})$, $-cycloalkyl(R_7)(R_{11})$, $-heterocyclyl(R_8)(R_{12})$, $-aryl(R_8)(R_{12})$ and $-heteroaryl(R_8)(R_{12})$;

R_{11} is selected from the group consisting of $-C_{1-8}alkyl(R_{13})$, $-O-C_{1-8}alkyl(R_{13})$, $-NH-C_{1-8}alkyl(R_{13})$, $-S-C_{1-8}alkyl(R_{13})$, $-C(=O)C_{1-8}alkyl(R_{13})$, $-O-C(=O)C_{1-8}alkyl(R_{13})$, $-NH-C(=O)C_{1-8}alkyl(R_{13})$, $-C(=O)OC_{1-8}alkyl(R_{13})$, $-C(=O)NHC_{1-8}alkyl(R_{13})$, $-O-C(=O)OC_{1-8}alkyl(R_{13})$, $-O-C(=O)NHC_{1-8}alkyl(R_{13})$, $-NH-C(=O)OC_{1-8}alkyl(R_{13})$, $-NH-C(=O)NHC_{1-8}alkyl(R_{13})$, $-C(=O)C_{1-8}alkylC(=O)(R_{13})$, $-O-C(=O)C_{1-8}alkylC(=O)(R_{13})$, $-NH-C(=O)C_{1-8}alkylC(=O)(R_{13})$, $-C(=O)OC_{1-8}alkylC(=O)(R_{13})$, $-O-C(=O)OC_{1-8}alkylC(=O)(R_{13})$, $-NH-C(=O)OC_{1-8}alkylC(=O)(R_{13})$, $-C(=O)NHC_{1-8}alkylC(=O)(R_{13})$, $-O-C(=O)NHC_{1-8}alkylC(=O)(R_{13})$, $-NH-C(=O)NHC_{1-8}alkylC(=O)(R_{13})$, $-OCH_2CH_2O(CH_2CH_2O)_rCH_2CH_2(R_{13})$,

$-NHCH_2CH_2O(CH_2CH_2O)_rCH_2CH_2(R_{13})$,
$-SCH_2CH_2O(CH_2CH_2O)_rCH_2CH_2(R_{13})$,
$-OCH_2CH_2O(CH_2CH_2O)_rCH_2C(=O)(R_{13})$,
$-NHCH_2CH_2O(CH_2CH_2O)_rCH_2C(=O)(R_{13})$,
$-SCH_2CH_2O(CH_2CH_2O)_rCH_2C(=O)(R_{13})$,
$-OC(=O)CH_2O(CH_2CH_2O)_rCH_2CH_2(R_{13})$,
$-OC(=O)OCH_2CH_2O(CH_2CH_2O)_rCH_2CH_2(R_{13})$,
$-OC(=O)NHCH_2CH_2O(CH_2CH_2O)_rCH_2CH_2(R_{13})$,
$-NH(C=O)CH_2O(CH_2CH_2O)_rCH_2CH_2(R_{13})$,
$-NHC(=O)OCH_2CH_2O(CH_2CH_2O)_rCH_2CH_2(R_{13})$,
$-NHC(=O)NHCH_2CH_2O(CH_2CH_2O)_rCH_2CH_2(R_{13})$,
$-SO_2CH_2CH_2O(CH_2CH_2O)_rCH_2CH_2(R_{13})$,
$-SO_2NHCH_2CH_2O(CH_2CH_2O)_rCH_2CH_2(R_{13})$,
$-C(=O)CH_2O(CH_2CH_2O)_rCH_2C(=O)(R_{13})$,
$-OC(=O)CH_2O(CH_2CH_2O)_rCH_2C(=O)(R_{13})$,
$-OC(=O)OCH_2CH_2O(CH_2CH_2O)_rCH_2C(=O)(R_{13})$,
$-OC(=O)NHCH_2CH_2O(CH_2CH_2O)_rCH_2C(=O)(R_{13})$,
$-NH(C=O)CH_2O(CH_2CH_2O)_rCH_2C(=O)(R_{13})$,
$-NHC(=O)OCH_2CH_2O(CH_2CH_2O)_rCH_2C(=O)(R_{13})$,
$-NHC(=O)NHCH_2CH_2O(CH_2CH_2O)_rCH_2C(=O)(R_{13})$,
$-SO_2CH_2CH_2O(CH_2CH_2O)_rCH_2C(=O)(R_{13})$, and
$-SO_2NHCH_2CH_2O(CH_2CH_2O)_rCH_2C(=O)(R_{13})$;

R_{12} is selected from the group consisting of $-C_{1-8}alkyl(R_{13})$, $-O-C_{1-8}alkyl(R_{13})$, $-NH-C_{1-8}alkyl(R_{13})$, $-S-C_{1-8}alkyl(R_{13})$, $-CH_2O-C_{1-8}alkyl(R_{13})$, $-CH_2NH-C_{1-8}alkyl(R_{13})$, $-CH_2S-C_{1-8}alkyl(R_{13})$, $-C(=O)C_{1-8}alkyl(R_{13})$, $-O-C(=O)C_{1-8}alkyl(R_{13})$, $-NH-C(=O)C_{1-8}alkyl(R_{13})$, $-CH_2O-C(=O)C_{1-8}alkyl(R_{13})$, $-CH_2NH-C(=O)C_{1-8}alkyl(R_{13})$, $-C(=O)OC_{1-8}alkyl(R_{13})$, $-C(=O)NHC_{1-8}alkyl(R_{13})$, $-O-C(=O)OC_{1-8}alkyl(R_{13})$, $-O-C(=O)NHC_{1-8}alkyl(R_{13})$, $-NH-C(=O)OC_{1-8}alkyl(R_{13})$, $-NH-C(=O)NHC_{1-8}alkyl(R_{13})$, $-CH_2O-C(=O)OC_{1-8}alkyl(R_{13})$, $-CH_2O-C(=O)NHC_{1-8}alkyl(R_{13})$,

$-CH_2NH-C(=O)OC_{1-8}alkyl(R_{13})$, $-CH_2NH-C(=O)NHC_{1-8}alkyl(R_{13})$, $-C(=O)C_{1-8}alkylC(=O)(R_{13})$, $-O-C(=O)C_{1-8}alkylC(=O)(R_{13})$, $-NH-C(=O)C_{1-8}alkylC(=O)(R_{13})$, $-CH_2O-C(=O)C_{1-8}alkylC(=O)(R_{13})$, $-CH_2NH-C(=O)C_{1-8}alkylC(=O)(R_{13})$, $-C(=O)OC_{1-8}alkylC(=O)(R_{13})$, $-O-C(=O)OC_{1-8}alkylC(=O)(R_{13})$, $-NH-C(=O)OC_{1-8}alkylC(=O)(R_{13})$, $-CH_2O-C(=O)OC_{1-8}alkylC(=O)(R_{13})$, $-CH_2NH-C(=O)OC_{1-8}alkylC(=O)(R_{13})$, $-C(=O)NHC_{1-8}alkylC(=O)(R_{13})$, $-O-C(=O)NHC_{1-8}alkylC(=O)(R_{13})$, $-NH-C(=O)NHC_{1-8}alkylC(=O)(R_{13})$, $-CH_2O-C(=O)NHC_{1-8}alkylC(=O)(R_{13})$, $-CH_2NH-C(=O)NHC_{1-8}alkylC(=O)(R_{13})$,

$-OCH_2CH_2O(CH_2CH_2O)_rCH_2CH_2(R_{13})$,

$-NHCH_2CH_2O(CH_2CH_2O)_rCH_2CH_2(R_{13})$,

$-SCH_2CH_2O(CH_2CH_2O)_rCH_2CH_2(R_{13})$,

$-OCH_2CH_2O(CH_2CH_2O)_rCH_2C(=O)(R_{13})$,

$-NHCH_2CH_2O(CH_2CH_2O)_rCH_2C(=O)(R_{13})$,

$-SCH_2CH_2O(CH_2CH_2O)_rCH_2C(=O)(R_{13})$,

$-OC(=O)CH_2O(CH_2CH_2O)_rCH_2CH_2(R_{13})$,

$-OC(=O)OCH_2CH_2O(CH_2CH_2O)_rCH_2CH_2(R_{13})$,

$-OC(=O)NHCH_2CH_2O(CH_2CH_2O)_rCH_2CH_2(R_{13})$,

$-NH(C=O)CH_2O(CH_2CH_2O)_rCH_2CH_2(R_{13})$,

$-NHC(=O)OCH_2CH_2O(CH_2CH_2O)_rCH_2CH_2(R_{13})$,

$-NHC(=O)NHCH_2CH_2O(CH_2CH_2O)_rCH_2CH_2(R_{13})$,

$-SO_2CH_2CH_2O(CH_2CH_2O)_rCH_2CH_2(R_{13})$,

$-SO_2NHCH_2CH_2O(CH_2CH_2O)_rCH_2CH_2(R_{13})$,

$-CH_2OCH_2CH_2O(CH_2CH_2O)_rCH_2CH_2(R_{13})$,

$-CH_2NHCH_2CH_2O(CH_2CH_2O)_rCH_2CH_2(R_{13})$,

$-CH_2SCH_2CH_2O(CH_2CH_2O)_rCH_2CH_2(R_{13})$,

$-CH_2OCH_2CH_2O(CH_2CH_2O)_rCH_2C(=O)(R_{13})$,

$-CH_2NHCH_2CH_2O(CH_2CH_2O)_rCH_2C(=O)(R_{13})$,

$-CH_2SCH_2CH_2O(CH_2CH_2O)_rCH_2C(=O)(R_{13})$,

$-CH_2OC(=O)CH_2O(CH_2CH_2O)_rCH_2CH_2(R_{13})$,

$-CH_2OC(=O)OCH_2CH_2O(CH_2CH_2O)_rCH_2CH_2(R_{13})$,

$-CH_2OC(=O)NHCH_2CH_2O(CH_2CH_2O)_rCH_2CH_2(R_{13})$,

-$CH_2NH(C=O)CH_2O(CH_2CH_2O)_rCH_2CH_2(R_{13})$,

-$CH_2NHC(=O)OCH_2CH_2O(CH_2CH_2O)_rCH_2CH_2(R_{13})$,

-$CH_2NHC(=O)NHCH_2CH_2O(CH_2CH_2O)_rCH_2CH_2(R_{13})$,

-$C(=O)CH_2O(CH_2CH_2O)_rCH_2C(=O)(R_{13})$,

-$OC(=O)CH_2O(CH_2CH_2O)_rCH_2C(=O)(R_{13})$,

-$OC(=O)OCH_2CH_2O(CH_2CH_2O)_rCH_2C(=O)(R_{13})$,

-$OC(=O)NHCH_2CH_2O(CH_2CH_2O)_rCH_2C(=O)(R_{13})$,

-$NH(C=O)CH_2O(CH_2CH_2O)_rCH_2C(=O)(R_{13})$,

-$NHC(=O)OCH_2CH_2O(CH_2CH_2O)_rCH_2C(=O)(R_{13})$,

-$NHC(=O)NHCH_2CH_2O(CH_2CH_2O)_rCH_2C(=O)(R_{13})$,

-$SO_2CH_2CH_2O(CH_2CH_2O)_rCH_2C(=O)(R_{13})$,

-$SO_2NHCH_2CH_2O(CH_2CH_2O)_rCH_2C(=O)(R_{13})$,

-$CH_2OC(=O)CH_2O(CH_2CH_2O)_rCH_2C(=O)(R_{13})$,

-$CH_2OC(=O)OCH_2CH_2O(CH_2CH_2O)_rCH_2C(=O)(R_{13})$,

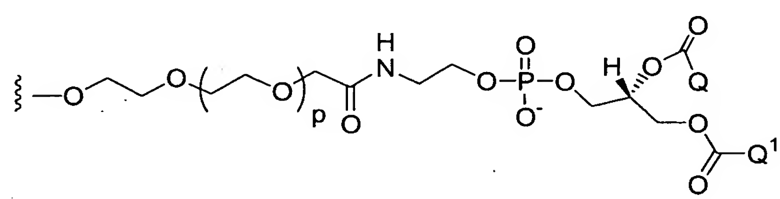
-$CH_2OC(=O)NHCH_2CH_2O(CH_2CH_2O)_rCH_2C(=O)(R_{13})$,

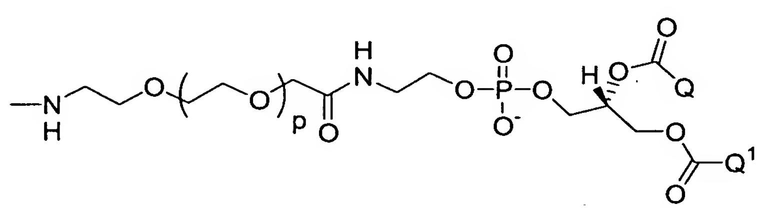
-$CH_2NH(C=O)CH_2O(CH_2CH_2O)_rCH_2C(=O)(R_{13})$,

-$CH_2NHC(=O)OCH_2CH_2O(CH_2CH_2O)_rCH_2C(=O)(R_{13})$, and

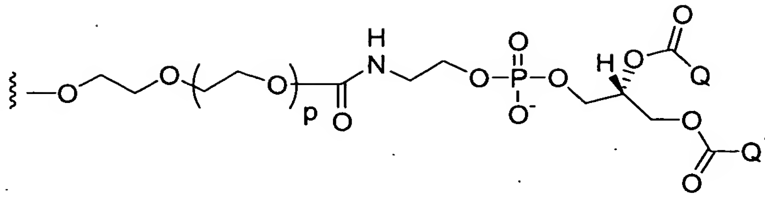
-$CH_2NHC(=O)NHCH_2CH_2O(CH_2CH_2O)_rCH_2C(=O)(R_{13})$;

wherein when R_{11} or R_{12} terminates with a $-C(=O)-$, R_{13} is selected from

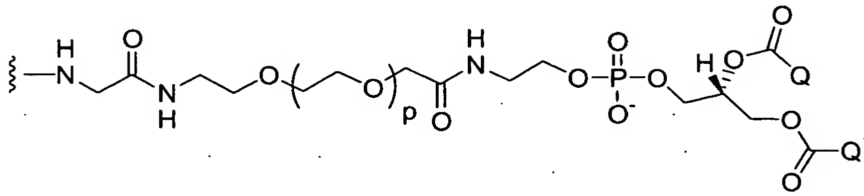




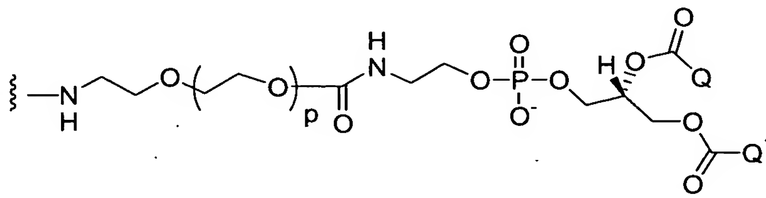
,



,

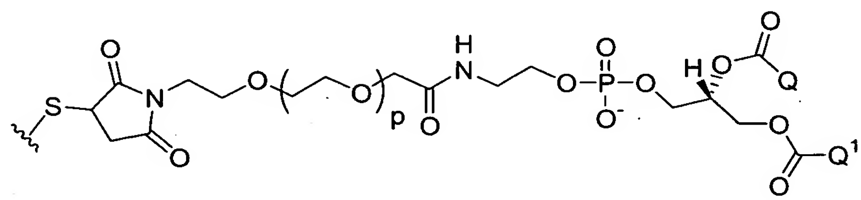


, or

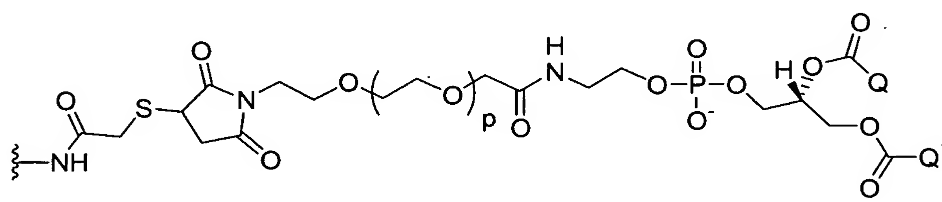


;

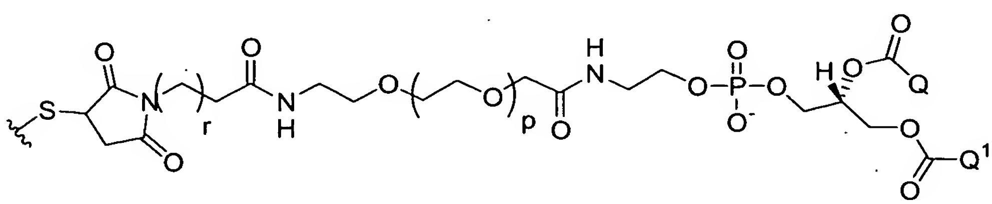
and when R_{11} or R_{12} does not terminate with a –C(=O)-, R_{13} is selected from the group consisting of



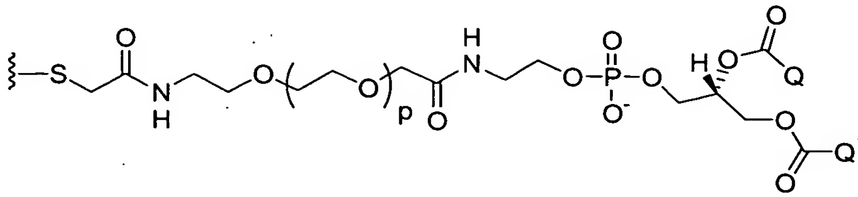
,

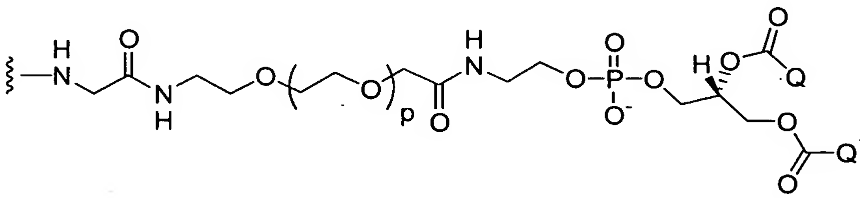


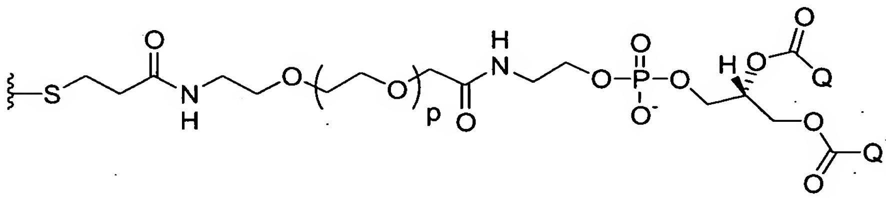
,

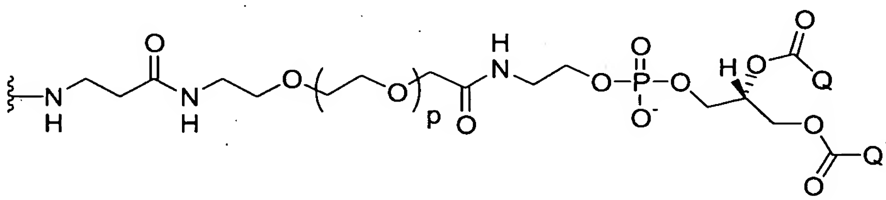


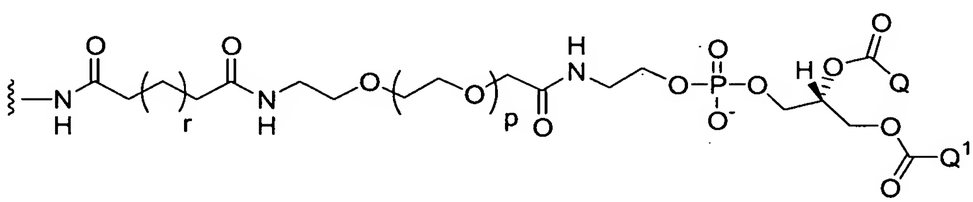
,

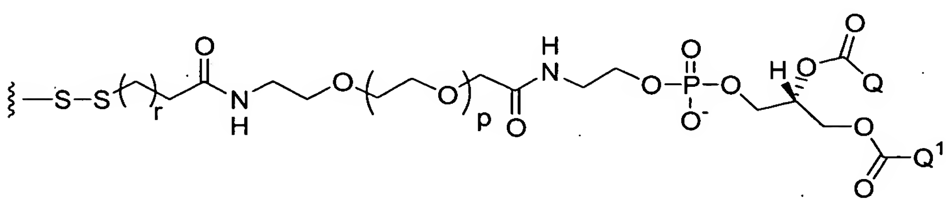

,

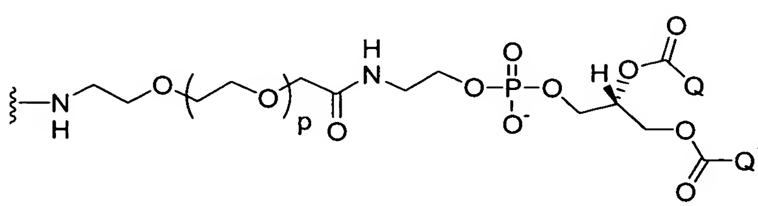

,

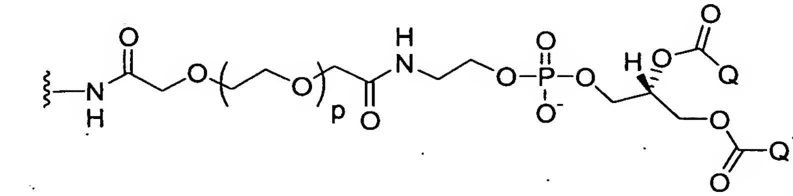

,

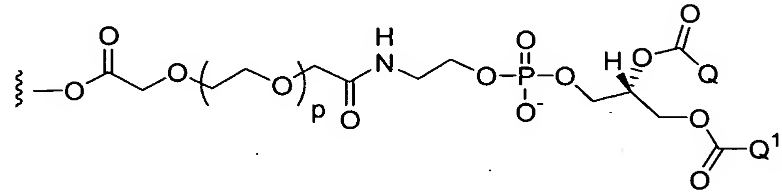

,

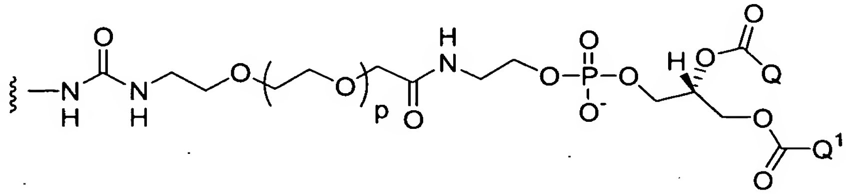

,

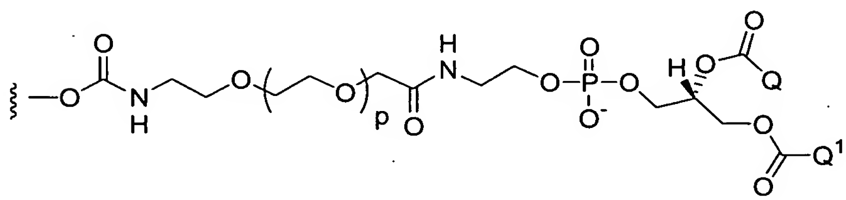

,

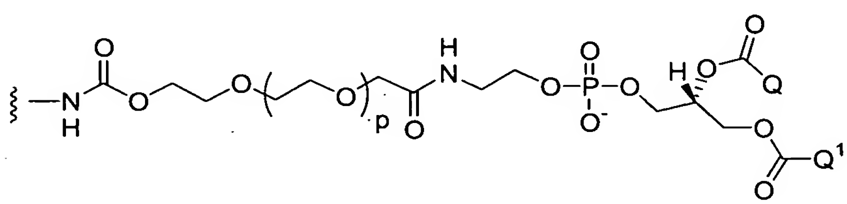

,

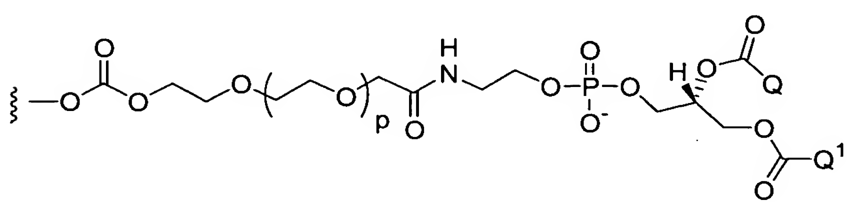

,

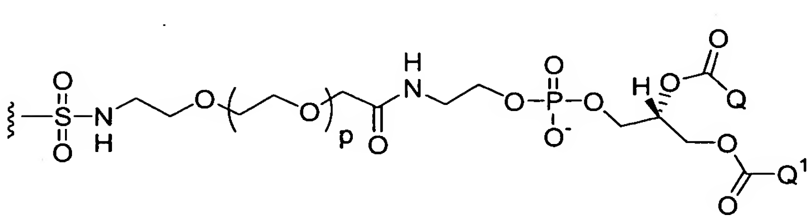

,

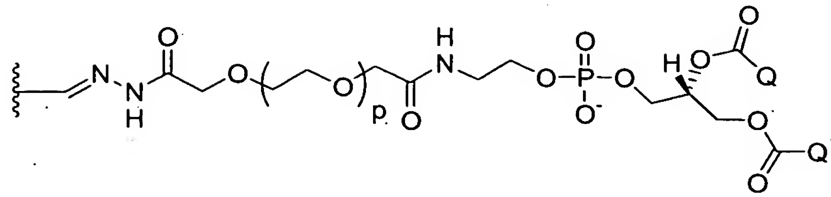

,

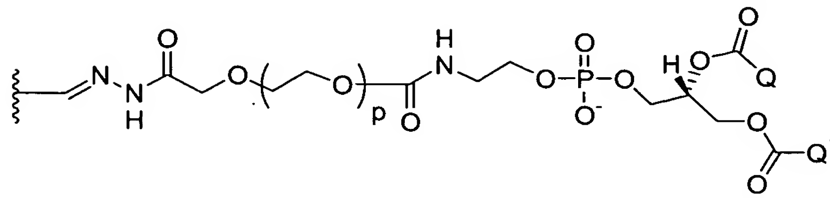

,

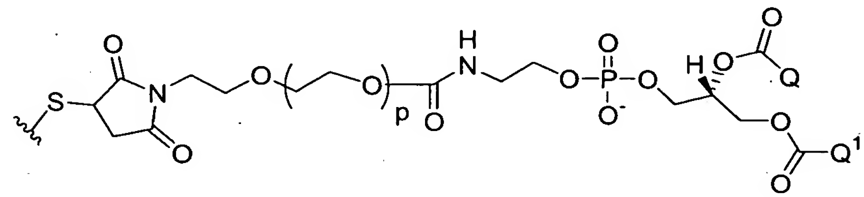

,

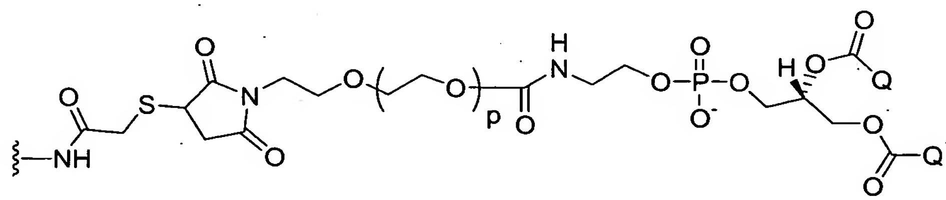

,

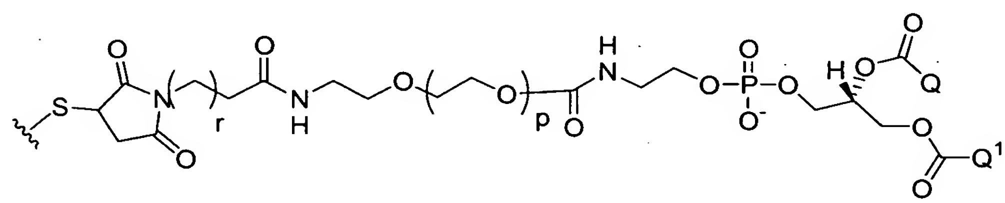


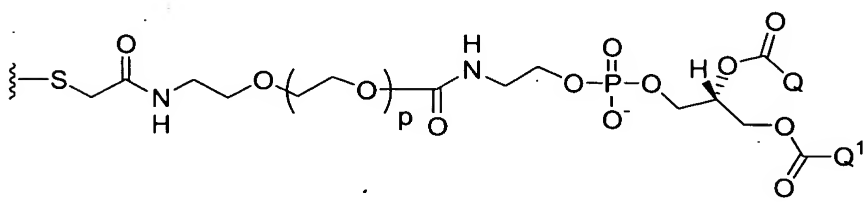

,

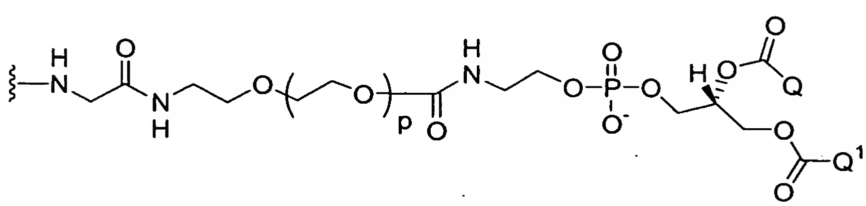

,

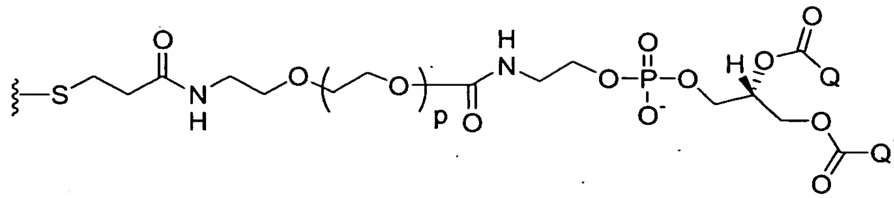

,


,

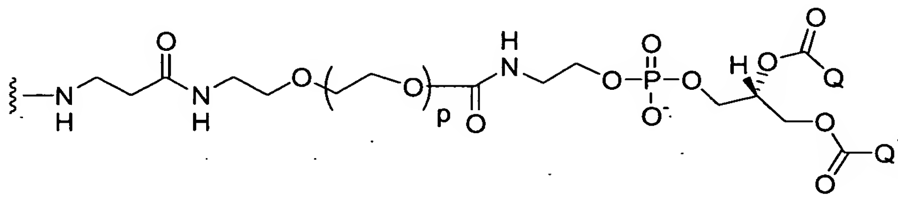

,


,

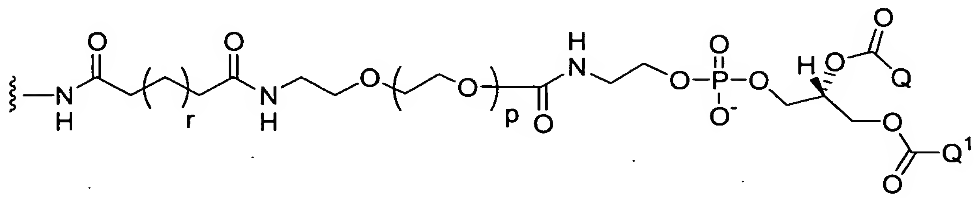

,



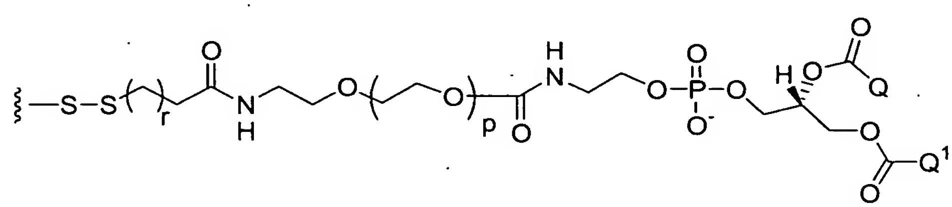
,



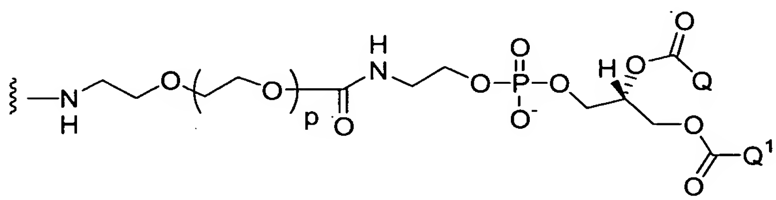
,



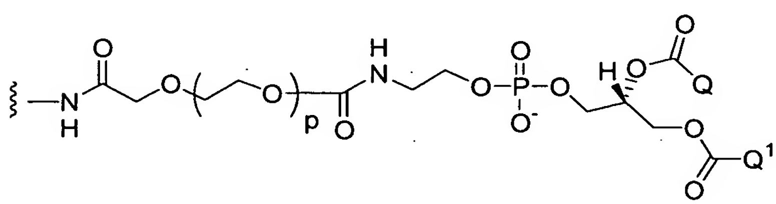
,



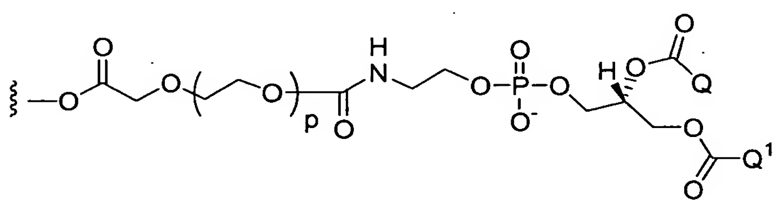
,



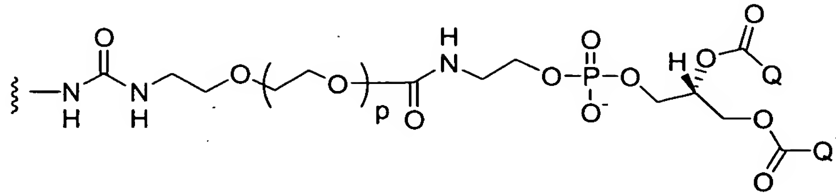
,

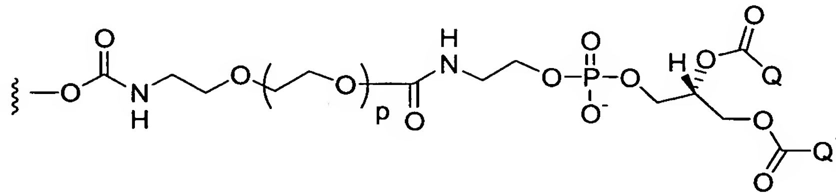


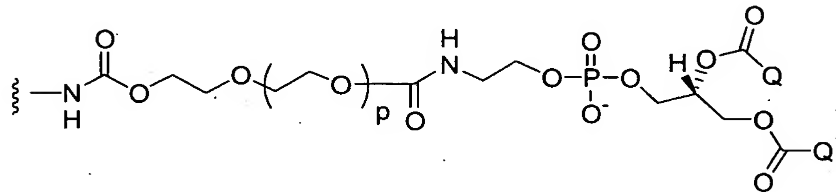
,

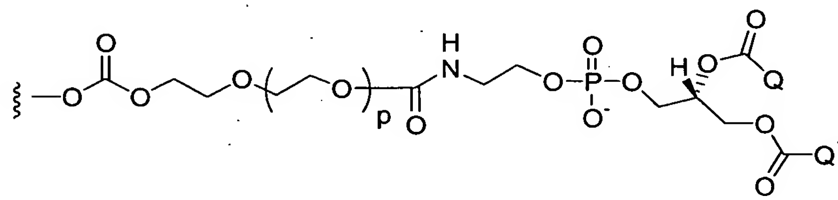


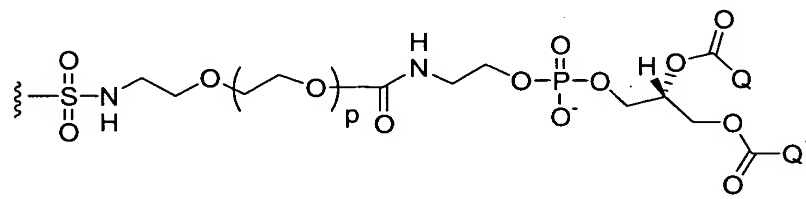
,

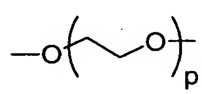

,


,


,


, and


;

wherein the unit $–O-(CH_2CH_2O-)_p-$ or  of R_{12} and R_{13} is a polyethylene glycol (PEG) polymer ranging in molecular weight from 750 to 5000 daltons;

r is an integer from 0 to 8;

Q and Q^1 of substituents R_{12} and R_{13} are the same within a given compound and are selected from the group consisting of

the C_{11} saturated chain of lauric acid,
the C_{13} saturated chain of myristoic acid,
the C_{15} saturated chain of palmitoic acid,
the C_{17} saturated chain of stearoic acid,
the C_{17} mono-unsaturated chain of oleoic acid, and
the C_{17} di-unsaturated chain of linoleic acid;

Z is selected from the group consisting of hydroxy, $-NH_2$, $-NH-C_{1-8}$alkyl, $-N(C_{1-8}alkyl)_2$, $-O-C_{1-8}$alkyl, $-O-C_{1-8}$alkyl-OH, $-O-C_{1-8}$alkylC_{1-8}alkoxy, -O-C_{1-8}alkylcarbonylC_{1-8}alkyl, $-O-C_{1-8}$alkyl-CO_2H, $-O-C_{1-8}$alkyl-C(O)O-C_{1-8}alkyl, -O-C_{1-8}alkyl-O-C(O)C_{1-8}alkyl, $-O-C_{1-8}$alkyl-NH_2, $-O-C_{1-8}$alkyl-NH-C_{1-8}alkyl, -O-C_{1-8}alkyl-N(C_{1-8}alkyl$)_2$, $-O-C_{1-8}$alkylamide, $-O-C_{1-8}$alkyl-C(O)-NH-C_{1-8}alkyl, -O-C_{1-8}alkyl-C(O)-N(C_{1-8}alkyl$)_2$, and –NHC(O)C_{1-8}alkyl;

and pharmaceutically acceptable salts, racemic mixtures and enantiomers thereof.

Another aspect of the present invention includes a therapeutic liposome composition sensitized to a target cell, comprising liposomes having an entrapped therapeutic agent, the liposomes including one or more targeting conjugates. The targeting conjugates have a structure represented by Formula (I) or Formula (II), and are comprised of (a) a lipid having a polar head group and a hydrophobic tail, (b) a hydrophilic polymer having a proximal end and a distal end, where the polymer is attached at its proximal end to the head group of the lipid, and (c) a piperidinoyl carboxylic acid compound attached to the distal end of the polymer.

BRIEF DESCRIPTION OF THE FIGURES

Figs. 1A-1B are HPLC chromatograms of a maleimide-poly(ethylene glycol)-distearoylphosphatidylethanolamine (Mal-PEG-DSPE) compound before conjugation (Fig. 1A) and after conjugation (Fig. 1B) to Compound 38b (Example 39) to form a DSPE-PEG-piperidinoyl carboxylic acid compound conjugate.

DETAILED DESCRIPTION OF THE INVENTION

1. Compounds

Another aspect of the present invention includes compounds of Formula (I) and Formula (II) wherein W is preferably is selected from the group consisting of $-C_{0-4}alkyl(R_1)$, $-C_{1-4}alkyl(R_{1a})$, $-C_{0-4}alkyl\text{-}aryl(R_1,R_8)$, $-C_{0-4}alkyl\text{-}heterocyclyl(R_1,R_8)$, $-C_{0-4}alkoxy(R_1)$, $-C_{0-4}alkoxy\text{-}aryl(R_1,R_8)$, and $-C_{0-4}alkoxy\text{-}heterocyclyl(R_1,R_8)$.

Aspects of the present invention include compounds of Formula (I) and Formula (II) wherein W is preferably $-C_{0-4}alkyl(R_1)$ or $-C_{0-4}alkyl\text{-}aryl(R_1,R_8)$.

Another aspect of the present invention includes compounds of Formula (I) and Formula (II) wherein W is preferably $-C_{0-4}alkyl(R_1)$ or $-C_{0-4}alkyl\text{-}phenyl(R_1,R_8)$.

Aspects of the present invention include compounds of Formula (I) and Formula (II) wherein R_1 is $-N(R_4)(R_6)$, -heterocyclyl(R_8) or -heteroaryl(R_8).

Another aspect of the present invention includes compounds of Formula (I) and Formula (II) wherein R_1 is $-N(R_4)(R_6)$, -dihydro-1*H*-pyrrolo[2,3-*b*]pyridinyl(R_8), -tetrahydropyrimidinyl(R_8), -tetrahydro-1,8-naphthyridinyl(R_8), -tetrahydro-1*H*-azepino[2,3-*b*]pyridinyl(R_8) or -pyridinyl(R_8).

Another aspect of the present invention includes compounds of Formula (I) and Formula (II) wherein R_1 is $-N(R_4)(R_6)$, -tetrahydropyrimidinyl(R_8) or -tetrahydro-1,8-naphthyridinyl(R_8).

Aspects of the present invention include compounds of Formula (I) and Formula (II) wherein R_{1a} is $-C(R_4)(=N\text{-}R_4)$, $-C(=N\text{-}R_4)\text{-}N(R_4)_2$, $-C(=N\text{-}R_4)\text{-}N(R_4)(R_6)$, $-C(=N\text{-}R_4)\text{-}N(R_4)\text{-}C(=O)\text{-}R_4$, $-C(=N\text{-}R_4)\text{-}N(R_4)\text{-}C(=O)\text{-}N(R_4)_2$, $-C(=N\text{-}R_4)\text{-}N(R_4)\text{-}CO_2\text{-}R_4$, $-C(=N\text{-}R_4)\text{-}N(R_4)\text{-}SO_2\text{-}C_{1-4}alkyl(R_7)$ or $-C(=N\text{-}R_4)\text{-}N(R_4)\text{-}SO_2\text{-}N(R_4)_2$.

Aspects of the present invention include compounds of Formula (I) and Formula (II) wherein R_4 is hydrogen or -C_{1-4}alkyl(R_7).

Another aspect of the present invention includes compounds of Formula (I) and Formula (II) wherein R_4 is hydrogen.

Aspects of the present invention include compounds of Formula (I) and Formula (II) wherein R_5 is -C(=O)-R_4, -C(=O)-N(R_4)$_2$, -C(=O)-cycloalkyl(R_8), -C(=O)-heterocyclyl(R_8), -C(=O)-aryl(R_8), -C(=O)-heteroaryl(R_8), -C(=O)-N(R_4)-cycloalkyl(R_8), -C(=O)-N(R_4)-aryl(R_8), -CO_2-R_4, -CO_2-cycloalkyl(R_8), -CO_2-aryl(R_8), -C(R_4)(=N-R_4), -C(=N-R_4)-N(R_4)$_2$, -C(=N-R_4)-N(R_4)(R_6), -C(=N-R_4)-N(R_4)-C(=O)-R_4, -C(=N-R_4)-N(R_4)-C(=O)-N(R_4)$_2$, -C(=N-R_4)-N(R_4)-CO_2-R_4, -C(=N-R_4)-N(R_4)-SO_2-C_{1-4}alkyl(R_7), -C(=N-R_4)-N(R_4)-SO_2-N(R_4)$_2$, -N(R_4)-C(R_4)(=N-R_4), -N(R_4)-C(=N-R_4)-N(R_4)$_2$, -N(R_4)-C(=N-R_4)-N(R_4)(R_6), -N(R_4)-C(=N-R_4)-N(R_4)-C(=O)-R_4, -N(R_4)-C(=N-R_4)-N(R_4)-C(=O)-N(R_4)$_2$, -N(R_4)-C(=N-R_4)-N(R_4)-CO_2-R_4, -N(R_4)-C(=N-R_4)-N(R_4)-SO_2-C_{1-4}alkyl(R_7), -N(R_4)-C(=N-R_4)-N(R_4)-SO_2-N(R_4)$_2$, -SO_2-C_{1-4}alkyl(R_7), -SO_2-N(R_4)$_2$, -SO_2-cycloalkyl(R_8) or -SO_2-aryl(R_8).

Another aspect of the present invention includes compounds of Formula (I) and Formula (II) wherein R_5 is -C(=O)-R_4, -C(=O)-N(R_4)$_2$, -CO_2-R_4, -C(R_4)(=N-R_4), -C(=N-R_4)-N(R_4)$_2$, -C(=N-R_4)-N(R_4)(R_6), -N(R_4)-C(R_4)(=N-R_4), -N(R_4)-C(=N-R_4)-N(R_4)$_2$, -N(R_4)-C(=N-R_4)-N(R_4)(R_6), -SO_2-C_{1-4}alkyl(R_7) or -SO_2-N(R_4)$_2$.

Aspects of the present invention include compounds of Formula (I) and Formula (II) wherein R_6 is -heterocyclyl(R_8) or -heteroaryl(R_8).

Another aspect of the present invention includes compounds of Formula (I) and Formula (II) wherein R_6 is -dihydroimidazolyl(R_8), -tetrahydropyridinyl(R_8), -tetrahydropyrimidinyl(R_8) or -pyridinyl(R_8).

Aspects of the present invention include compounds of Formula (I) and Formula (II) wherein R_7 is one to two substituents independently selected from hydrogen, $-C_{1-4}$alkoxy(R_9), $-NH_2$, $-NH-C_{1-4}$alkyl(R_9), $-N(C_{1-4}$alkyl(R_9))$_2$, -C(=O)H, $-C(=O)-C_{1-4}$alkyl(R_9), $-C(=O)-NH_2$, $-C(=O)-NH-C_{1-4}$alkyl(R_9), $-C(=O)-N(C_{1-4}$alkyl(R_9))$_2$, -C(=O)-NH-aryl(R_{10}), -C(=O)-cycloalkyl(R_{10}), -C(=O)-heterocyclyl(R_{10}), -C(=O)-aryl(R_{10}), -C(=O)-heteroaryl(R_{10}), $-CO_2H$, $-CO_2-C_{1-4}$alkyl(R_9), $-CO_2$-aryl(R_{10}), $-C(=NH)-NH_2$, -SH, $-S-C_{1-4}$alkyl(R_9), $-S-C_{1-4}$alkyl$-S-C_{1-4}$alkyl(R_9), $-S-C_{1-4}$alkyl$-C_{1-4}$alkoxy(R_9), $-S-C_{1-4}$alkyl$-NH-C_{1-4}$alkyl(R_9), $-SO_2-C_{1-4}$alkyl(R_9), $-SO_2-NH_2$, $-SO_2-NH-C_{1-4}$alkyl(R_9), $-SO_2-N(C_{1-4}$alkyl(R_9))$_2$, $-SO_2$-aryl(R_{10}), cyano, (halo)$_{1-3}$, hydroxy, nitro, oxo, -cycloalkyl(R_{10}), -heterocyclyl(R_{10}), -aryl(R_{10}) or -heteroaryl(R_{10}).

Another aspect of the present invention includes compounds of Formula (I) and Formula (II) wherein R_7 is one to two substituents independently selected from hydrogen, $-C_{1-4}$alkoxy(R_9), $-NH_2$, $-NH-C_{1-4}$alkyl(R_9), $-N(C_{1-4}$alkyl(R_9))$_2$, (halo)$_{1-3}$, hydroxy or oxo.

A further aspect of the present invention includes compounds of Formula (I) and Formula (II) wherein R_7 is hydrogen.

Aspects of the present invention include compounds of Formula (I) and Formula (II) wherein R_8 is one to four substituents independently selected from hydrogen, $-C_{1-4}$alkyl(R_9), -C(=O)H, $-C(=O)-C_{1-4}$alkyl(R_9), $-C(=O)-NH_2$, $-C(=O)-NH-C_{1-4}$alkyl(R_9), $-C(=O)-N(C_{1-4}$alkyl(R_9))$_2$, -C(=O)-NH-aryl(R_{10}), -C(=O)-cycloalkyl(R_{10}), -C(=O)-heterocyclyl(R_{10}), -C(=O)-aryl(R_{10}), -C(=O)-heteroaryl(R_{10}), $-CO_2H$, $-CO_2-C_{1-4}$alkyl(R_9), $-CO_2$-aryl(R_{10}), $-C(=NH)-NH_2$, $-SO_2-C_{1-4}$alkyl(R_9), $-SO_2-NH_2$, $-SO_2-NH-C_{1-4}$alkyl(R_9), $-SO_2-N(C_{1-4}$alkyl(R_9))$_2$, $-SO_2$-aryl(R_{10}), -cycloalkyl(R_{10}) or -aryl(R_{10}) when attached to a nitrogen atom; and, wherein R_8 is one to four substituents independently selected from hydrogen, $-C_{1-4}$alkyl(R_9), $-C_{1-4}$alkoxy(R_9), -O-cycloalkyl(R_{10}), -O-aryl(R_{10}), -C(=O)H, $-C(=O)-C_{1-4}$alkyl(R_9), $-C(=O)-NH_2$, $-C(=O)-NH-C_{1-4}$alkyl(R_9),

$-C(=O)-N(C_{1-4}alkyl-R_{11})_2$, $-C(=O)-NH-aryl(R_{10})$, $-C(=O)-cycloalkyl(R_{10})$, $-C(=O)-heterocyclyl(R_{10})$, $-C(=O)-aryl(R_{10})$, $-C(=O)-heteroaryl(R_{10})$, $-CO_2H$, $-CO_2-C_{1-4}alkyl(R_9)$, $-CO_2-aryl(R_{10})$, $-C(=NH)-NH_2$, $-SO_2-C_{1-4}alkyl(R_9)$, $-SO_2-NH_2$, $-SO_2-NH-C_{1-4}alkyl(R_9)$, $-SO_2-N(C_{1-4}alkyl(R_9))_2$, $-SO_2-aryl(R_{10})$, -SH, $-S-C_{1-4}alkyl(R_9)$, $-S-C_{1-4}alkyl-S-C_{1-4}alkyl(R_9)$, $-S-C_{1-4}alkyl-C_{1-4}alkoxy(R_9)$, $-S-C_{1-4}alkyl-NH-C_{1-4}alkyl(R_9)$, $-NH_2$, $-NH-C_{1-4}alkyl(R_9)$, $-N(C_{1-4}alkyl(R_9))_2$, cyano, halo, hydroxy, nitro, oxo, $-cycloalkyl(R_{10})$, $-heterocyclyl(R_{10})$, $-aryl(R_{10})$ or $-heteroaryl(R_{10})$ when attached to a carbon atom.

Another aspect of the present invention includes compounds of Formula (I) and Formula (II) wherein R_8 is one to four substituents independently selected from hydrogen, $-C_{1-4}alkyl(R_9)$, $-C(=O)H$, $-C(=O)-NH_2$, $-C(=O)-NH-C_{1-4}alkyl(R_9)$, $-C(=O)-N(C_{1-4}alkyl(R_9))_2$, $-CO_2H$, $-CO_2-C_{1-4}alkyl(R_9)$ or $-SO_2-NH_2$ when attached to a nitrogen atom; and, wherein R_8 is one to four substituents independently selected from hydrogen, $-C_{1-4}alkyl(R_9)$, $-C_{1-4}alkoxy(R_9)$, $-O-aryl(R_{10})$, $-C(=O)H$, $-C(=O)-NH_2$, $-C(=O)-NH-C_{1-4}alkyl(R_9)$, $-C(=O)-N(C_{1-4}alkyl(R_9))_2$, $-CO_2H$, $-CO_2-C_{1-4}alkyl(R_9)$, $-SO_2-NH_2$, $-NH_2$, $-NH-C_{1-4}alkyl(R_9)$, $-N(C_{1-4}alkyl(R_9))_2$, cyano, halo, hydroxy, nitro or oxo when attached to a carbon atom.

Another aspect of the present invention includes compounds of Formula (I) and Formula (II) wherein R_8 is one to four substituents independently selected from hydrogen or $-C_{1-4}alkyl(R_9)$ when attached to a nitrogen atom; and, wherein R_8 is one to four substituents independently selected from hydrogen, $-C_{1-4}alkyl(R_9)$, $-C_{1-4}alkoxy(R_9)$, $-O-aryl(R_{10})$, $-NH_2$, $-NH-C_{1-4}alkyl(R_9)$, $-N(C_{1-4}alkyl(R_9))_2$, halo, hydroxy or oxo when attached to a carbon atom.

A further aspect of the present invention includes compounds of Formula (I) and Formula (II) wherein R_8 is one to four substituents independently selected from hydrogen or $-C_{1-4}alkyl(R_9)$ when attached to a nitrogen atom; and, wherein R_8 is one to four substituents independently selected from hydrogen, $-C_{1-4}alkyl(R_9)$, $-C_{1-4}alkoxy(R_9)$ $-O-aryl(R_{10})$ or hydroxy when attached to a carbon atom.

Aspects of the present invention include compounds of Formula (I) and Formula (II) wherein R_9 is hydrogen, $-C_{1-4}$alkoxy, $-NH_2$, $-NH-C_{1-4}$alkyl, $-N(C_{1-4}alkyl)_2$, $-C(=O)H$, $-C(=O)-NH_2$, $-C(=O)-NH-C_{1-4}$alkyl, $-C(=O)-N(C_{1-4}alkyl)_2$, $-CO_2H$, $-CO_2-C_{1-4}$alkyl, $-SO_2-C_{1-4}$alkyl, $-SO_2-NH_2$, $-SO_2-NH-C_{1-4}$alkyl, $-SO_2-N(C_{1-4}alkyl)_2$, cyano, $(halo)_{1-3}$, hydroxy, nitro or oxo.

Another aspect of the present invention includes compounds of Formula (I) and Formula (II) wherein R_9 is hydrogen, $-C_{1-4}$alkoxy, $-NH_2$, $-NH-C_{1-4}$alkyl, $-N(C_{1-4}alkyl)_2$, $-C(=O)H$, $-CO_2H$, $-C(=O)-C_{1-4}$alkoxy, $(halo)_{1-3}$, hydroxy or oxo.

A further aspect of the present invention includes compounds of Formula (I) wherein R_9 is hydrogen, $-C_{1-4}$alkoxy, $-NH_2$, $-NH-C_{1-4}$alkyl, $-N(C_{1-4}alkyl)_2$, $(halo)_{1-3}$ or hydroxy.

Aspects of the present invention include compounds of Formula (I) and Formula (II) wherein R_{10} is one to four substituents independently selected from hydrogen, $-C_{1-4}$alkyl, $-C(=O)H$, $-C(=O)-C_{1-4}$alkyl, $-C(=O)-NH_2$, $-C(=O)-NH-C_{1-4}$alkyl, $-C(=O)-N(C_{1-4}alkyl)_2$, $-CO_2H$, $-CO_2-C_{1-4}$alkyl, $-SO_2-C_{1-4}$alkyl, $-SO_2-NH_2$, $-SO_2-NH-C_{1-4}$alkyl or $-SO_2-N(C_{1-4}alkyl)_2$ when attached to a nitrogen atom; and, wherein R_{10} is one to four substituents independently selected from hydrogen, $-C_{1-4}$alkyl, $-C_{1-4}$alkoxy, $-C(=O)H$, $-C(=O)-C_{1-4}$alkyl, $-C(=O)-NH_2$, $-C(=O)-NH-C_{1-4}$alkyl, $-C(=O)-N(C_{1-4}alkyl)_2$, $-CO_2H$, $-CO_2-C_{1-4}$alkyl, $-SO_2-C_{1-4}$alkyl, $-SO_2-NH_2$, $-SO_2-NH-C_{1-4}$alkyl, $-SO_2-N(C_{1-4}alkyl)_2$, $-NH_2$, $-NH-C_{1-4}$alkyl, $-N(C_{1-4}alkyl)_2$, cyano, halo, hydroxy, nitro or oxo when attached to a carbon atom.

Another aspect of the present invention includes compounds of Formula (I) and Formula (II) wherein $(R_{10})_{1-4}$ is hydrogen, $-C_{1-4}$alkyl, $-C_{1-4}$alkoxy, $-C(=O)H$, $-C(=O)-C_{1-4}$alkyl, $-CO_2H$, $-CO_2-C_{1-4}$alkyl, $-NH_2$, $-NH-C_{1-4}$alkyl, $-N(C_{1-4}alkyl)_2$, halo, hydroxy, nitro or oxo when attached to a carbon atom.

A further aspect of the present invention includes compounds of Formula (I) and Formula (II) wherein R_{10} is hydrogen.

Aspects of the present invention include compounds of Formula (I) and Formula (II) wherein R_2 is hydrogen, -C_{1-4}alkyl(R_7), -C_{2-4}alkenyl(R_7), -C_{2-4}alkynyl(R_7), -cycloalkyl(R_8), -heterocyclyl(R_8), -aryl(R_8) or -heteroaryl(R_8).

Another aspect of the present invention includes compounds of Formula (I) and Formula (II) wherein R_2 is hydrogen, -cycloalkyl(R_8), -heterocyclyl(R_8), -aryl(R_8) or -heteroaryl(R_8).

Another aspect of the present invention includes compounds of Formula (I) and Formula (II) wherein R_2 is hydrogen, -cycloalkyl(R_8), -heterocyclyl(R_8), -phenyl(R_8), -naphthalenyl(R_8) or -heteroaryl(R_8).

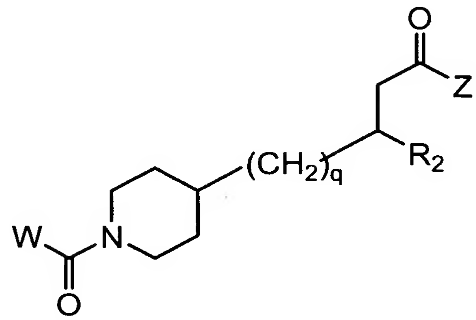
Another aspect of the present invention includes compounds of Formula (I) and Formula (II) wherein R_2 is hydrogen, -tetrahydropyrimidinyl(R_8), -1,3-benzodioxolyl(R_8), -dihydrobenzofuranyl(R_8), -tetrahydroquinolinyl(R_8), -phenyl(R_8), -naphthalenyl(R_8), -pyridinyl(R_8), -pyrimidinyl(R_8) or -quinolinyl(R_8).

For the targeting ligand and targeting conjugates previously decribed R_2 is replaced by R_{2A}, which is described hereinafter.

Aspects of the present invention include a composition comprising a compound of Formula (I) and Formula (II) wherein q is 1, 2 or 3.

Aspects of the present invention include a composition comprising a compound of Formula (I) and Formula (II) wherein Z is selected from the group consisting of hydroxy, -NH_2, -NH-C_{1-8}alkyl, -N(C_{1-8}alkyl)$_2$, -O-C_{1-8}alkyl, -O-C_{1-8}alkyl-OH, -O-C_{1-8}alkylC_{1-4}alkoxy, -O-C_{1-8}alkylcarbonylC_{1-4}alkyl, -O-C_{1-8}alkyl-CO_2H, -O-C_{1-8}alkyl-C(O)O-C_{1-6}alkyl, -O-C_{1-8}alkyl-O-C(O)C_{1-8}alkyl, -O-C_{1-8}alkyl-NH_2, -O-C_{1-8}alkyl-NH-C_{1-8}alkyl, -O-C_{1-8}alkyl-N(C_{1-8}alkyl)$_2$, –O-C_{1-8}alkylamide -O-C_{1-8}alkyl-C(O)-NH-C_{1-8}alkyl, -O-C_{1-8}alkyl-C(O)-N(C_{1-8}alkyl)$_2$ and –NHC(O)C_{1-8}alkyl..

Aspects of the present invention include a composition comprising compound of Formula (I)



Formula (I)

wherein the compound is selected from the group consisting of:

Cpd	W	R_1	R_2	q	Stereo chem	Z
1	$-CH_2-Ph(3-R_1)$	-NH-1,4,5,6-tetrahydro-pyrimidin-2-yl	H	0		OH
2	$-(CH_2)_2-Ph(3-R_1)$	-NH-1,4,5,6-tetrahydro-pyrimidin-2-yl	H	0		OH
3	$-CH_2-Ph(3-R_1)$	-NH-1,4,5,6-tetrahydro-5-OH-pyrimidin-2-yl	quinolin-3-yl	0		OH
4	$-(CH_2)_3-R_1$	5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl	quinolin-3-yl	0		OH
5	$-(CH_2)_3-R_1$	5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl	1,2,3,4-tetrahydro-quinolin-3-yl	0		OH
5-1	$-(CH_2)_3-R_1$	5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl	1,2,3,4-tetrahydro-quinolin-3-yl	0	Isomer 1	OH
5-2	$-(CH_2)_3-R_1$	5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl	1,2,3,4-tetrahydro-quinolin-3-yl	0	Isomer 2	OH

Cpd	W	R_1	R_2	q	Stereo chem	Z
5-3	$-(CH_2)_3-R_1$	5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl	1,2,3,4-tetrahydro-quinolin-3-yl	0	Isomer 3	OH
5-4	$-(CH_2)_3-R_1$	5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl	1,2,3,4-tetrahydro-quinolin-3-yl	0	Isomer 4	OH
6	$Ph(3-R_1)$	-NH-1,4,5,6-tetrahydro-pyrimidin-2-yl	pyridin-3-yl	2		OH
7	$Ph(3-R_1)$	-NH-1,4,5,6-tetrahydro-5-OH-pyrimidin-2-yl	pyridin-3-yl	2		OH
8	$-(CH_2)_2-R_1$	5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl	pyridin-3-yl	2		OH
9	$-(CH_2)_3-R_1$	-NH-pyridin-2-yl	pyridin-3-yl	2		OH
10	$Ph(3-R_1)$	-NH-1,4,5,6-tetrahydro-5-OH-pyrimidin-2-yl	$(6-OCH_3)$-pyridin-3-yl	2		OH
11	$-(CH_2)_2-R_1$	5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl	1,3-benzodioxol-5-yl	1		OH
12	$Ph(3-R_1)$	-NH-1,4,5,6-tetrahydro-pyrimidin-2-yl	quinolin-3-yl	2		OH
13	$-(CH_2)_2-R_1$	5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl	phenyl	1		OH
14	$-(CH_2)_2-R_1$	5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl	1,3-benzodioxol-5-yl	0		OH
15	$-(CH_2)_3-R_1$	5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl	1,3-benzodioxol-5-yl	0		OH
16	$-CH_2-R_1$	5,6,7,8-tetrahydro-[1,8]naphthyridin-2-	1,3-benzodioxol-5-yl	0		OH

Cpd	W	R_1	R_2	q	Stereo chem	Z
		yl				
17	$-(CH_2)_3-R_1$	5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl	($6-OCH_3$)-pyridin-3-yl	0		OH
18	$-(CH_2)_2-R_1$	5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl	1,4,5,6-tetrahydro-2-Me-pyrimidin-5-yl	1		OH
19	$-(CH_2)_2-R_1$	5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl	1,2,3,4-tetrahydro-quinolin-3-yl	1		OH
19-1	$-(CH_2)_2-R_1$	5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl	1,2,3,4-tetrahydro-quinolin-3-yl	1	Isomer 1	OH
19-2	$-(CH_2)_2-R_1$	5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl	1,2,3,4-tetrahydro-quinolin-3-yl	1	Isomer 2	OH
19-3	$-(CH_2)_2-R_1$	5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl	1,2,3,4-tetrahydro-quinolin-3-yl	1	Isomer 3	OH
19-4	$-(CH_2)_2-R_1$	5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl	1,2,3,4-tetrahydro-quinolin-3-yl	1	Isomer 4	OH
20	$-(CH_2)_2-R_1$	5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl	1,3-benzodioxol-5-yl	2		OH
21	$-(CH_2)_2-R_1$	5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl	($6-OCH_3$)-pyridin-3-yl	2		OH
21a	$-(CH_2)_2-R_1$	5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl	($6-OCH_3$)-pyridin-3-yl	2	Isomer a	OH
21b	$-(CH_2)_2-R_1$	5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl	($6-OCH_3$)-pyridin-3-yl	2	Isomer b	OH

Cpd	W	R_1	R_2	q	Stereo chem	Z
22	$-(CH_2)_3-R_1$	-NH-pyridin-2-yl	quinolin-3-yl	2		OH
23	$-(CH_2)_3-R_1$	-NH-pyridin-2-yl	1,3-benzodioxol-5-yl	2		OH
24	$-(CH_2)_3-R_1$	-NH-pyridin-2-yl	1,3-benzodioxol-5-yl	0		OH
25	$-(CH_2)_3-R_1$	-NH-pyridin-2-yl	(6-OCH_3)-pyridin-3-yl	2		OH
26	$-(CH_2)_3-R_1$	5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl	1,3-benzodioxol-5-yl	1		OH
27	Ph(3-R_1)	-NH-1,4,5,6-tetrahydro-5-OH-pyrimidin-2-yl	1,3-benzodioxol-5-yl	1		OH
28	$-(CH_2)_2-R_1$	5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl	(6-OCH_3)-pyridin-3-yl	1		OH
28a	$-(CH_2)_2-R_1$	5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl	(6-OCH_3)-pyridin-3-yl	1	Isomer a	OH
28b	$-(CH_2)_2-R_1$	5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl	(6-OCH_3)-pyridin-3-yl	1	Isomer b	OH
29	$-(CH_2)_3-R_1$	5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl	quinolin-3-yl	1		OH
30	$-(CH_2)_2-R_1$	5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl	(3-F)phenyl	1		OH
30a	$-(CH_2)_2-R_1$	5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl	(3-F)phenyl	1	Isomer a	OH
30b	$-(CH_2)_2-R_1$	5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl	(3-F)phenyl	1	Isomer b	OH

Cpd	W	R_1	R_2	q	Stereo chem	Z
31	$-(CH_2)_3-R_1$	5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl	(3-F)phenyl	1		OH
32	$-(CH_2)_2-R_1$	5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl	quinolin-3-yl	1		OH
33	$-(CH_2)_2-R_1$	5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl	(4-F)phenyl	1		OH
34	$-(CH_2)_3-R_1$	5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl	(4-F)phenyl	1		OH
35	$-(CH_2)_2-R_1$	5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl	$(2-CH_3)$pyrimidin-5-yl	1		OH
36	$-(CH_2)_2-R_1$	5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl	2,3-dihydro-benzofuran-6-yl	1		OH
36a	$-(CH_2)_2-R_1$	5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl	2,3-dihydro-benzofuran-6-yl	1	Isomer a	OH
36b	$-(CH_2)_2-R_1$	5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl	2,3-dihydro-benzofuran-6-yl	1	Isomer b	OH
37	$-(CH_2)_2-R_1$	5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl	(3,5-difluoro)-phenyl	1		OH
38	$-(CH_2)_3-R_1$	5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl	(3,5-difluoro)-phenyl	1		OH
39	$-(CH_2)_2-R_1$	5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl	$(3-CF_3)$-phenyl	1		OH
40	$-(CH_2)_2-R_1$	5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl	$(4-OCF_3)$-phenyl	1		OH

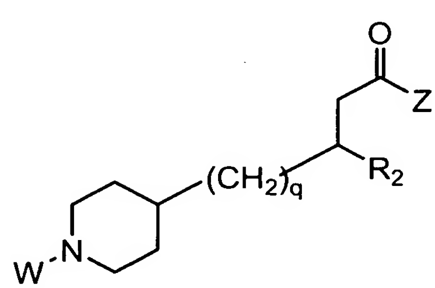
Cpd	W	R_1	R_2	q	Stereo chem	Z
41	$-(CH_2)_2-R_1$	5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl	(3-F-4-Ph)-phenyl	1		OH
42	$-(CH_2)_2-R_1$	5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl	(3-F-4-OCH_3)-phenyl	1		OH
43	$-(CH_2)_2-R_1$	5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl	(4-Oph)-phenyl	1		OH
44	$-(CH_2)_2-R_1$	5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl	isoquinolin-4-yl	1		OH
45	$-(CH_2)_2-R_1$	5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl	pyridin-3-yl	1		OH
46	$-(CH_2)_2-R_1$	5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl	dihydrobenzofuran-5-yl	1		OH
47	$-(CH_2)_2-R_1$	5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl	(2,4-OCH_3)-pyrimidin-5-yl	1		OH
48	$-(CH_2)_2-R_1$	5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl	(2-OCH_3)-pyrimidin-5-yl	1		OH
49	Ph(3-R_1)	-NH-1,4,5,6-tetrahydro-5-OH-pyrimidin-2-yl	quinolin-3-yl	2		OH
50	Ph(3-R_1)	-NH-1,4,5,6-tetrahydro-pyridin-2-yl	quinolin-3-yl	2		OH
51	$-(CH_2)_2-R_1$	5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl	quinolin-3-yl	2		OH
52	Ph(3-R_1)	-NH-3,4,5,6-tetrahydro-pyrimidin-2-yl	1,3-benzodioxol-5-yl	2		OH

Cpd	W	R_1	R_2	q	Stereo chem	Z
53	Ph(3-R_1)	-NH-3,4,5,6-tetrahydro-pyridin-2-yl	1,3-benzodioxol-5-yl	2		OH
54	Ph(3-R_1)	NH-1,4,5,6-tetrahydro-5-OH-pyrimidin-2-yl	1,3-benzodioxol-5-yl	2		OH
55	$-CH_2-R_1$	5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl	1,3-benzodioxol-5-yl	2		OH
56	$-(CH_2)_2-R_1$	5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl	naphthalene-2-yl	1		OH
56a	$-(CH_2)_2-R_1$	5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl	naphthalen-2-yl	1	Isomer a	OH
56b	$-(CH_2)_2-R_1$	5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl	naphthalen-2-yl	1	Isomer b	OH
57	$-(CH_2)_2-R_1$	5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl	5,6,7,8-tetrahydro-quinolin-3-yl	1	racemic	OH
58a	$-(CH_2)_3-R_1$	5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl	5,6,7,8-tetrahydro-quinolin-3-yl	0	Isomer a	OH
58b	$-(CH_2)_3-R_1$	5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl	5,6,7,8-tetrahydro-quinolin-3-yl	0	Isomer b	OH
59	$-(CH_2)_2-R$	5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl	(3-OCH_3)phenyl	1	racemic	OH
60	$-(CH_2)_2-R_1$	5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl	(4-OCH_3)phenyl	1	racemic	OH
61	$-(CH_2)_2-R_1$	5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl	H	1		OH

Cpd	W	R_1	R_2	q	Stereo chem	Z
62	$-(CH_2)_2-R_1$	5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl	tetrahydrofuran-3-yl	1	racemic	OH
63	$-(CH_2)_2-R_1$	5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl	thiophen-2-yl	1	racemic	OH
64	$-(CH_2)_2-R_1$	5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl	(3-F)phenyl	1	racemic	NH_2
65	$-(CH_2)_2-R_1$	5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl	2,3-dihydro-benzo[1,4]-dioxin-6-yl	1	racemic	OH
66	$-(CH_2)_2-R_1$	5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl	(3-SCH_3)phenyl	1	racemic	OH
67	$-(CH_2)_2-R_1$	5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl	*N*-methyl-1,2,3,4-tetrahydro-quinolin-3-yl	1	racemic	OH
68	$-(CH_2)_2-R_1$	5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl	H	1		-O-ethyl
69	$-(CH_2)_2-R_1$	5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl	H	1		-O-2-propyl
70	$-(CH_2)_2-R_1$	5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl	H	1		-*O*-*t*-butyl
71	$-(CH_2)_2-R_1$	5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl	H	1		-*O*-*n*-octyl
72	$-(CH_2)_2-R_1$	5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl	H	1		-*O*-*s*-butyl
73	$-(CH_2)_2-R_1$	5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl	H	1		-O--methyl

Cpd	W	R_1	R_2	q	Stereo chem	Z
74	$-(CH_2)_2-R_1$	5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl	H	1	racemic	$-O-CH_2-OC(O)-t$-butyl
75	$-(CH_2)_2-R_1$	5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl	$(3-(NMe_2)$phenyl	1	racemic	OH
76	$-(CH_2)_2-R_1$	5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl	(3-OMe-4-OH)phenyl	1	racemic	OH
76a	$-(CH_2)_2-R_1$	5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl	(3-OMe-4-OH)phenyl	1	Isomer a	OH
77	$Ph(3-R_1)$	-NH-4,5-dihydro-1*H*-imidazol-2-yl	(3-F)phenyl	1	racemic	OH
78	$-(CH_2)_2-R_1$	5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl	(3-NHEt)phenyl	1	racemic	OH
79	$-(CH_2)_2-R_1$	5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl	(3-NHMe)phenyl	1	racemic	OH
80	$-(CH_2)_3-R_1$	5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl	dihydrobenzofuran-6-yl	0		OH

Aspects of the present invention include a composition comprising a compound of Formula (II)



Formula (II)

wherein W, R_1, R_2, q and Z are as previously defined and preferably are

Cpd	W	R_1	R_2	q	Stereo chem	Z
81	$-(CH_2)_3-R_1$	5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl	(3-F)phenyl	1	racemic	OH

Aspects of the present invention include a composition comprising a compound of Formula (I) wherein the compound is selected from the group consisting of

a compound of Formula (I) wherein W is $-CH_2-Ph(3-R_1)$; R_1 is -NH-1,4,5,6-tetrahydro-pyrimidin-2-yl; R_2 is H, q is 0 and Z is OH;

a compound of Formula (I) wherein W is $-(CH_2)_2-Ph(3-R_1)$; R_1 is -NH-1,4,5,6-tetrahydro-pyrimidin-2-yl; R_2 is H, q is 0 and Z is OH;

a compound of Formula (I) wherein W is $-CH_2-Ph(3-R_1)$; R_1 is -NH-1,4,5,6-tetrahydro-5-OH-pyrimidin-2-yl; R_2 is -3-quinolinyl, q is 0 and Z is OH;

a compound of Formula (I) wherein W is $-(CH_2)_3-R_1$; R_1 is -5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl; R_2 is -3-quinolinyl, q is 0 and Z is OH;

a compound of Formula (I) wherein W is $-(CH_2)_3-R_1$; R_1 is -5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl; R_2 is -1,2,3,4-tetrahydro-3-quinolinyl, q is 0 and Z is OH

a compound of Formula (I) wherein W is $-Ph(3-R_1)$; R_1 is -NH-1,4,5,6-tetrahydro-pyrimidin-2-yl; R_2 is -3-pyridinyl, q is 2 and Z is OH;

a compound of Formula (I) wherein W is $-Ph(3-R_1)$; R_1 is -NH-1,4,5,6-tetrahydro-5-OH-pyrimidin-2-yl; R_2 is -3-pyridinyl, q is 2 and Z is OH;

a compound of Formula (I) wherein W is $-(CH_2)_2-R_1$; R_1 is -5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl; R_2 is -3-pyridinyl, q is 2 and Z is OH;

a compound of Formula (I) wherein W is $-(CH_2)_3-R_1$; R_1 is -NH-pyridin-2-yl; R_2 is -3-pyridinyl, q is 2, and Z is OH;

a compound of Formula (I) wherein W is $-Ph(3-R_1)$; R_1 is -NH-1,4,5,6-tetrahydro-5-OH-pyrimidin-2-yl; R_2 is -(6-MeO)pyridin-3-yl, q is 2 and Z is OH;

a compound of Formula (I) wherein W is -$(CH_2)_2$-R_1; R_1 is -5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl; R_2 is -1,3-benzodioxol-5-yl, q is 1 and Z is OH;

a compound of Formula (I) wherein W is -Ph(3-R_1); R_1 is -NH-1,4,5,6-tetrahydro-pyrimidin-2-yl; R_2 is -3-quinolinyl, q is 2 and Z is OH;

a compound of Formula (I) wherein W is -$(CH_2)_2$-R_1; R_1 is -5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl; R_2 is -Ph, q is 1 and Z is OH;

a compound of Formula (I) wherein W is -$(CH_2)_2$-R_1; R_1 is -5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl; R_2 is -1,3-benzodioxol-5-yl, q is 0 and Z is OH;

a compound of Formula (I) wherein W is -$(CH_2)_3$-R_1; R_1 is -5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl; R_2 is -1,3-benzodioxol-5-yl, q is 0 and Z is OH;

a compound of Formula (I) wherein W is -CH_2-R_1; R_1 is -5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl; R_2 is -1,3-benzodioxol-5-yl, q is 0 and Z is OH;

a compound of Formula (I) wherein W is -$(CH_2)_3$-R_1; R_1 is -5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl; R_2 is -(6-MeO)pyridin-3-yl, q is 0 and Z is OH;

a compound of Formula (I) wherein W is -$(CH_2)_2$-R_1; R_1 is -5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl; R_2 is -1,4,5,6-tetrahydro-2-Me-pyrimidin-5-yl, q is 1 and Z is OH;

a compound of Formula (I) wherein W is -$(CH_2)_2$-R_1; R_1 is -5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl; R_2 is -1,2,3,4-tetrahydro-3-quinolinyl, q is 1 and Z is OH;

a compound of Formula (I) wherein W is -$(CH_2)_2$-R_1; R_1 is -5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl; R_2 is -1,3-benzodioxol-5-yl, q is 2 and Z is OH;

a compound of Formula (I) wherein W is -$(CH_2)_2$-R_1; R_1 is -5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl; R_2 is -(6-MeO)pyridin-3-yl, q is 2 and Z is OH;

a compound of Formula (I) wherein W is -$(CH_2)_3$-R_1; R_1 is -NH-pyridin-2-yl; R_2 is

-3-quinolinyl, q is 2 and Z is OH;

a compound of Formula (I) wherein W is -$(CH_2)_3$-R_1; R_1 is -NH-pyridin-2-yl; R_2 is -1,3-benzodioxol-5-yl, q is 2 and Z is OH;

a compound of Formula (I) wherein W is -$(CH_2)_3$-R_1; R_1 is -NH-pyridin-2-yl; R_2 is -1,3-benzodioxol-5-yl, q is 0 and Z is OH;

a compound of Formula (I) wherein W is -$(CH_2)_3$-R_1; R_1 is -NH-pyridin-2-yl; R_2 is -(6-MeO)pyridin-3-yl, q is 2 and Z is OH;

a compound of Formula (I) wherein W is -$(CH_2)_3$-R_1; R_1 is -5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl; R_2 is -1,3-benzodioxol-5-yl, q is 1 and Z is OH;

a compound of Formula (I) wherein W is -Ph(3-R_1); R_1 is -NH-1,4,5,6-tetrahydro-5-OH-2-pyrimidinyl; R_2 is -1,3-benzodioxol-5-yl, q is 1 and Z is OH;

a compound of Formula (I) wherein W is -$(CH_2)_2$-R_1; R_1 is -5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl; R_2 is -(6-MeO)pyridin-3-yl, q is 1 and Z is OH;

a compound of Formula (I) wherein W is -$(CH_2)_3$-R_1; R_1 is -5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl; R_2 is -3-quinolinyl, q is 1 and Z is OH;

a compound of Formula (I) wherein W is -$(CH_2)_2$-R_1; R_1 is -5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl; R_2 is -(3-F)Ph, q is 1 and Z is OH;

a compound of Formula (I) wherein W is -$(CH_2)_3$-R_1; R_1 is -5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl; R_2 is -(3-F)Ph, q is 1 and Z is OH;

a compound of Formula (I) wherein W is -$(CH_2)_2$-R_1; R_1 is -5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl; R_2 is -3-quinolinyl, q is 1 and Z is OH;

a compound of Formula (I) wherein W is -$(CH_2)_2$-R_1; R_1 is -5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl; R_2 is -(4-F)Ph, q is 1 and Z is OH;

a compound of Formula (I) wherein W is -$(CH_2)_3$-R_1; R_1 is -5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl; R_2 is -(4-F)Ph, q is 1 and Z is OH;

a compound of Formula (I) wherein W is -$(CH_2)_2$-R_1; R_1 is -5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl; R_2 is -(2-Me)pyrimidin-5-yl, q is 1

and Z isOH;

a compound of Formula (I) wherein W is $-(CH_2)_2-R_1$; R_1 is -5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl; R_2 is -2,3-dihydro-benzofuran-6-yl, q is 1 and Z is OH;

a compound of Formula (I) wherein W is $-(CH_2)_2-R_1$; R_1 is -5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl; R_2 is $-(3,5-F_2)Ph$, q is 1 and Z is OH;

a compound of Formula (I) wherein W is $-(CH_2)_3-R_1$; R_1 is -5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl; R_2 is $-(3,5-F_2)Ph$, q is 1 and Z is OH;

a compound of Formula (I) wherein W is $-(CH_2)_2-R_1$; R_1 is -5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl; R_2 is $-(3-CF_3)Ph$, q is 1 and Z is OH;

a compound of Formula (I) wherein W is $-(CH_2)_2-R_1$; R_1 is -5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl; R_2 is $-(4-OCF_3)Ph$, q is 1 and Z is OH;

a compound of Formula (I) wherein W is $-(CH_2)_2-R_1$; R_1 is -5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl; R_2 is -(3-F-4-Ph)Ph, q is 1 and Z is OH;

a compound of Formula (I) wherein W is $-(CH_2)_2-R_1$; R_1 is -5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl; R_2 is -(3-F-4-OMe)Ph, q is 1, and Z is OH;

a compound of Formula (I) wherein W is $-(CH_2)_2-R_1$; R_1 is -5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl; R_2 is -(4-OPh)Ph, q is 1 and Z is OH;

a compound of Formula (I) wherein W is $-(CH_2)_2-R_1$; R_1 is -5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl; R_2 is -4-isoquinolinyl, q is 1, and Z is OH;

a compound of Formula (I) wherein W is $-(CH_2)_2-R_1$; R_1 is -5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl; R_2 is -3-pyridinyl, q is 1 and Z is OH;

a compound of Formula (I) wherein W is $-(CH_2)_2-R_1$; R_1 is -5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl; R_2 is -5-dihydrobenzofuranyl, q is 1 and Z is OH;

a compound of Formula (I) wherein W is $-(CH_2)_2-R_1$; R_1 is -5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl; R_2 is $-2,4-(OMe)_2$-pyrimid-5-yl, q is 1

and Z is OH;

a compound of Formula (I) wherein W is -$(CH_2)_2$-R_1; R_1 is -5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl; R_2 is -(2-OMe)pyrimidin-5-yl, q is 1 and Z is OH;

a compound of Formula (I) wherein W is -Ph(3-R_1); R_1 is -NH-1,4,5,6-tetrahydro-5-OH-pyrimidin-2-yl; R_2 is -3-quinolinyl, q is 2 and Z is OH;

a compound of Formula (I) wherein W is -Ph(3-R_1); R_1 is -NH-3,4,5,6-tetrahydro-pyridin-2-yl; R_2 is -3-quinolinyl, q is 2 and Z is OH;

a compound of Formula (I) wherein W is -$(CH_2)_2$-R_1; R_1 is -5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl; R_2 is -3-quinolinyl, q is 2 and Z is OH;

a compound of Formula (I) wherein W is -Ph(3-R_1); R_1 is -NH-3,4,5,6-tetrahydro-pyrimidin-2-yl; R_2 is -1,3-benzodioxol-5-yl, q is 2 and Z is OH;

a compound of Formula (I) wherein W is -Ph(3-R_1); R_1 is -NH-3,4,5,6-tetrahydro-pyridin-2-yl; R_2 is -1,3-benzodioxol-5-yl, q is 2 and Z is OH;

a compound of Formula (I) wherein W is -Ph(3-R_1); R_1 is -NH-1,4,5,6-tetrahydro-5-OH-pyrimidin-2-yl; R_2 is -1,3-benzodioxol-5-yl, q is 2 and Z is OH;

a compound of Formula (I) wherein W is -CH_2-R_1; R_1 is -5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl; R_2 is -1,3-benzodioxol-5-yl, q is 2 and Z is OH; and,

a compound of Formula (I) wherein W is -$(CH_2)_2$-R_1; R_1 is -5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl; R_2 is -2-naphthalenyl, q is 1 and Z is OH.

Another aspect of the present invention includes a composition comprising a compound of Formula (I) wherein the compound is selected from the group consisting of:

a compound of Formula (I) wherein W is -$(CH_2)_3$-R_1; R_1 is

-5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl; R_2 is -1,2,3,4-tetrahydro-3-quinolinyl, q is 0 and Z is OH;

a compound of Formula (I) wherein W is $-(CH_2)_3-R_1$; R_1 is -5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl; R_2 is -1,3-benzodioxol-5-yl, q is 0 and Z is OH;

a compound of Formula (I) wherein W is $-(CH_2)_2-R_1$; R_1 is -5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl; R_2 is -1,2,3,4-tetrahydro-3-quinolinyl, q is 1 and Z is OH;

a compound of Formula (I) wherein W is $-(CH_2)_2-R_1$; R_1 is -5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl; R_2 is -(6-MeO)pyridin-3-yl, q is 1 and Z is OH;

a compound of Formula (I) wherein W is $-(CH_2)_2-R_1$; R_1 is -5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl; R_2 is -(3-F)Ph, q is 1 and Z is OH;

a compound of Formula (I) wherein W is $-(CH_2)_2-R_1$; R_1 is -5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl; R_2 is -3-quinolinyl, q is 1 and Z is OH;

a compound of Formula (I) wherein W is $-(CH_2)_2-R_1$; R_1 is -5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl; R_2 is -(2-Me)pyrimidin-5-yl, q is 1 and Z is OH;

a compound of Formula (I) wherein W is $-(CH_2)_2-R_1$; R_1 is -5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl; R_2 is -2,3-dihydro-benzofuran-6-yl, q is 1 and Z is OH;

a compound of Formula (I) wherein W is $-(CH_2)_2-R_1$; R_1 is -5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl; R_2 is -4-isoquinolinyl, q is 1, and Z is OH;

a compound of Formula (I) wherein W is $-(CH_2)_2-R_1$; R_1 is -5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl; R_2 is -3-pyridinyl, q is 1 and Z is OH;

a compound of Formula (I) wherein W is $-(CH_2)_2-R_1$; R_1 is -5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl; R_2 is -2,4-$(OMe)_2$-pyrimid-5-yl, q is 1 and Z is OH; and,

a compound of Formula (I) wherein W is $-(CH_2)_2-R_1$; R_1 is

-5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl; R_2 is -(2-OMe)pyrimidin-5-yl, q is 1 and Z is OH.

Another aspect of the present invention includes a compound of Formula (I) wherein W is -$(CH_2)_3$-R_1; R_1 is -5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl; R_2 is -1,2,3,4-tetrahydro-3-quinolinyl, q is 0 and Z is OH.

Another aspect of the present invention includes a compound of Formula (I) wherein W is -$(CH_2)_3$-R_1; R_1 is -5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl; R_2 is -1,3-benzodioxol-5-yl, q is 0 and Z is OH.

Another aspect of the present invention includes a compound of Formula (I) wherein W is -$(CH_2)_2$-R_1; R_1 is -5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl; R_2 is -1,2,3,4-tetrahydro-3-quinolinyl, q is 1 and Z is OH; .

Another aspect of the present invention includes a compound of Formula (I) wherein W is -$(CH_2)_2$-R_1; R_1 is -5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl; R_2 is -(6-MeO)pyridin-3-yl, q is 1 and Z is OH.

Another aspect of the present invention includes a compound of Formula (I) wherein W is -$(CH_2)_2$-R_1; R_1 is -5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl; R_2 is -(3-F)Ph, q is 1 and Z is OH.

Another aspect of the present invention includes a compound of Formula (I) wherein W is -$(CH_2)_2$-R_1; R_1 is -5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl; R_2 is -3-quinolinyl, q is 1 and Z is OH.

Another aspect of the present invention includes a compound of Formula (I) wherein W is -$(CH_2)_2$-R_1; R_1 is -5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl; R_2 is -(2-Me)pyrimidin-5-yl, q is 1 and Z is OH.

Another aspect of the present invention includes a compound of Formula (I)

wherein W is $-(CH_2)_2-R_1$; R_1 is -5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl; R_2 is -2,3-dihydro-benzofuran-6-yl, q is 1 and Z is OH.

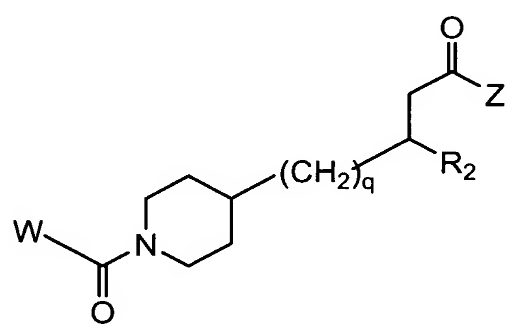
Another aspect of the present invention includes a compound of Formula (I) wherein W is $-(CH_2)_2-R_1$; R_1 is -5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl; R_2 is -4-isoquinolinyl, q is 1 and Z is OH.

Another aspect of the present invention includes a compound of Formula (I) wherein W is $-(CH_2)_2-R_1$; R_1 is -5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl; R_2 is -3-pyridinyl, q is 1 and Z is OH.

Another aspect of the present invention includes a compound of Formula (I) wherein W is $-(CH_2)_2-R_1$; R_1 is -5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl; R_2 is -2,4-$(OMe)_2$-pyrimid-5-yl, q is 1 and Z is OH.

Another aspect of the present invention includes a compound of Formula (I) wherein W is $-(CH_2)_2-R_1$; R_1 is -5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl; R_2 is -(2-OMe)pyrimidin-5-yl, q is 1 and Z is OH.

Aspects of the present invention include a compound of Formula (I):



Formula (I)

wherein W, R_1, R_2, R_6, R_8, R_9, q and Z are as previously defined; and, preferably, wherein

W is $-C_{0-4}alkyl(R_1)$ or $-C_{0-4}alkyl-phenyl(R_1,R_8)$;

R_1 is $-NH(R_6)$;

R_2 is hydrogen, -tetrahydropyrimidinyl(R_8), -1,3-benzodioxolyl(R_8), -dihydrobenzofuranyl(R_8), -tetrahydroquinolinyl(R_8), -phenyl(R_8), -naphthalenyl(R_8), -pyridinyl(R_8), -pyrimidinyl(R_8) or -quinolinyl(R_8);

R_6 is -dihydroimidazolyl(R_8), -tetrahydropyridinyl(R_8), -tetrahydropyrimidinyl(R_8) or -pyridinyl(R_8);

R_8 is one to four substituents independently selected from hydrogen or -$C_{1\text{-}4}$alkyl(R_9) when attached to a nitrogen atom; and, wherein R_8 is one to four substituents independently selected from hydrogen, -$C_{1\text{-}4}$alkyl(R_9), -$C_{1\text{-}4}$alkoxy(R_9), -O-aryl(R_{10}) or hydroxy when attached to a carbon atom;

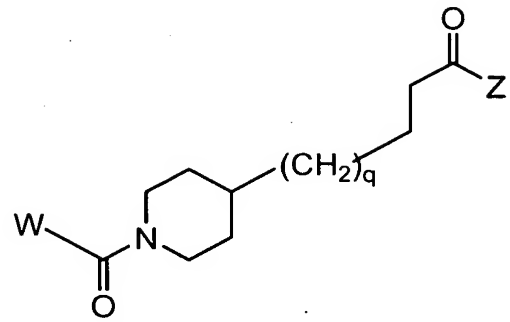
R_9 is hydrogen, -$C_{1\text{-}4}$alkoxy, -NH_2, -NH-$C_{1\text{-}4}$alkyl, -N($C_{1\text{-}4}$alkyl)$_2$, (halo)$_{1\text{-}3}$ or hydroxy; and,

q is 1, 2 or 3;

Z is selected from the group consisting of hydroxy, -NH_2, -NH-$C_{1\text{-}8}$alkyl, -N($C_{1\text{-}8}$alkyl)$_2$, -O-$C_{1\text{-}8}$alkyl, -O-$C_{1\text{-}8}$alkyl-OH, -O-$C_{1\text{-}8}$alkyl$C_{1\text{-}8}$alkoxy, -O-$C_{1\text{-}8}$alkylcarbonyl$C_{1\text{-}8}$alkyl, -O-$C_{1\text{-}8}$alkyl-CO_2H, -O-$C_{1\text{-}8}$alkyl-C(O)O-$C_{1\text{-}8}$alkyl, -O-$C_{1\text{-}8}$alkyl-O-C(O)$C_{1\text{-}8}$alkyl, -O-$C_{1\text{-}8}$alkyl-NH_2, -O-$C_{1\text{-}8}$alkyl-NH-$C_{1\text{-}8}$alkyl, -O-$C_{1\text{-}8}$alkyl-N($C_{1\text{-}8}$alkyl)$_2$, -O-$C_{1\text{-}8}$alkylamide, -O-$C_{1\text{-}8}$alkyl-C(O)-NH-$C_{1\text{-}8}$alkyl, -O-$C_{1\text{-}8}$alkyl-C(O)-N($C_{1\text{-}8}$alkyl)$_2$ and –NHC(O)$C_{1\text{-}8}$alkyl;

and pharmaceutically acceptable salts, racemic mixtures and enantiomers thereof.

Aspects of the present invention include a compound of Formula (I) wherein the compound is a compound of Formula (I.2):



Formula (I.2)

wherein W, R_1, R_6, R_8, R_9, q and Z are as previously defined; and, preferably, wherein W is -C_{0-4}alkyl(R_1) or -C_{0-4}alkyl-phenyl(R_1,R_8);

R_1 is -NH(R_6), -dihydro-1*H*-pyrrolo[2,3-*b*]pyridinyl(R_8), -tetrahydropyrimidinyl(R_8), -tetrahydro-1,8-naphthyridinyl(R_8), -tetrahydro-1*H*-azepino[2,3-*b*]pyridinyl(R_8) or -pyridinyl(R_8);

R_6 is -dihydroimidazolyl(R_8), -tetrahydropyridinyl(R_8), -tetrahydropyrimidinyl(R_8) or -pyridinyl(R_8);

R_8 is one to four substituents independently selected from hydrogen or -C_{1-4}alkyl(R_9) when attached to a nitrogen atom; and, wherein R_8 is one to four substituents independently selected from hydrogen, -C_{1-4}alkyl(R_9), -C_{1-4}alkoxy(R_9), -O-aryl(R_{10}) or hydroxy when attached to a carbon atom;

R_9 is hydrogen, -C_{1-4}alkoxy, -NH_2, -NH-C_{1-4}alkyl, -N(C_{1-4}alkyl)$_2$, (halo)$_{1-3}$ or hydroxy; and,

q is 1, 2 or 3;

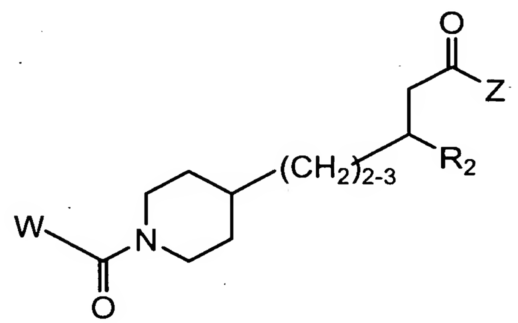
Z is selected from the group consisting hydroxy, -NH_2, -NH-C_{1-8}alkyl, -N(C_{1-8}alkyl)$_2$, -O-C_{1-8}alkyl, -O-C_{1-8}alkyl-OH, -O-C_{1-8}alkylC_{1-8}alkoxy, -O-C_{1-8}alkylcarbonylC_{1-8}alkyl, -O-C_{1-8}alkyl-CO_2H, -O-C_{1-8}alkyl-C(O)O-C_{1-8}alkyl, -O-C_{1-8}alkyl-O-C(O)C_{1-8}alkyl, -O-C_{1-8}alkyl-NH_2, -O-C_{1-8}alkyl-NH-C_{1-8}alkyl, -O-C_{1-8}alkyl-N(C_{1-8}alkyl)$_2$, -O-C_{1-8}alkylamide, -O-C_{1-8}alkyl-C(O)-NH-C_{1-8}alkyl, -O-C_{1-}

$_8$alkyl-C(O)-N(C_{1-8}alkyl)$_2$ and –NHC(O)C_{1-8}alkyl;

and pharmaceutically acceptable salts, racemic mixtures and enantiomers thereof.

Another aspect of the present invention includes compounds of Formula (I.2) wherein R_1 is -NH(R_6), -tetrahydropyrimidinyl(R_8) or -tetrahydro-1,8-naphthyridinyl(R_8); and, all other variables are as previously defined.

Aspects of the present invention include a compound of Formula (I) wherein the compound is a compound of Formula (I.3):



Formula (I.3)

wherein W, R_1, R_2, R_6, R_8, R_9 and Z are as previously defined; and, preferably, wherein

W is -C_{0-4}alkyl(R_1) or -C_{0-4}alkyl-phenyl(R_1,R_8);

R_1 is -NH(R_6), -dihydro-1*H*-pyrrolo[2,3-*b*]pyridinyl(R_8), -tetrahydropyrimidinyl(R_8), -tetrahydro-1,8-naphthyridinyl(R_8), -tetrahydro-1*H*-azepino[2,3-*b*]pyridinyl(R_8) or -pyridinyl(R_8);

R_2 is hydrogen, -tetrahydropyrimidinyl(R_8), -1,3-benzodioxolyl(R_8), -dihydrobenzofuranyl(R_8), -tetrahydroquinolinyl(R_8), -phenyl(R_8), -naphthalenyl(R_8), -pyridinyl(R_8), -pyrimidinyl(R_8) or -quinolinyl(R_8);

R_6 is -dihydroimidazolyl(R_8), -tetrahydropyridinyl(R_8), -tetrahydropyrimidinyl(R_8) or -pyridinyl(R_8);

R_8 is one to four substituents independently selected from hydrogen or -$C_{1\text{-}4}$alkyl(R_9) when attached to a nitrogen atom; and, wherein R_8 is one to four substituents independently selected from hydrogen, -$C_{1\text{-}4}$alkyl(R_9), -$C_{1\text{-}4}$alkoxy(R_9), -O-aryl(R_{10}) or hydroxy when attached to a carbon atom; and,

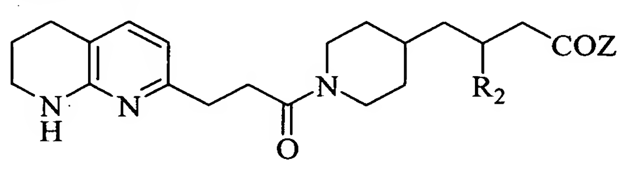
R_9 is hydrogen, -$C_{1\text{-}4}$alkoxy, -NH_2, -NH-$C_{1\text{-}4}$alkyl, -N($C_{1\text{-}4}$alkyl)$_2$, (halo)$_{1\text{-}3}$ or hydroxy;

Z is selected from the group consisting of hydroxy, -NH_2, -NH-$C_{1\text{-}8}$alkyl, -N($C_{1\text{-}8}$alkyl)$_2$, -O-$C_{1\text{-}8}$alkyl, -O-$C_{1\text{-}8}$alkyl-OH, -O-$C_{1\text{-}8}$alkyl$C_{1\text{-}8}$alkoxy, -O-$C_{1\text{-}8}$alkylcarbonyl$C_{1\text{-}8}$alkyl, -O-$C_{1\text{-}8}$alkyl-CO_2H, -O-$C_{1\text{-}8}$alkyl-C(O)O-$C_{1\text{-}8}$alkyl, -O-$C_{1\text{-}8}$alkyl-O-C(O)$C_{1\text{-}8}$alkyl, -O-$C_{1\text{-}8}$alkyl-NH_2, -O-$C_{1\text{-}8}$alkyl-NH-$C_{1\text{-}8}$alkyl, -O-$C_{1\text{-}8}$alkyl-N($C_{1\text{-}8}$alkyl)$_2$, -O-$C_{1\text{-}8}$alkylamide, -O-$C_{1\text{-}8}$alkyl-C(O)-NH-$C_{1\text{-}8}$alkyl, -O-$C_{1\text{-}8}$alkyl-C(O)-N($C_{1\text{-}8}$alkyl)$_2$ and –NHC(O)$C_{1\text{-}8}$alkyl;

and pharmaceutically acceptable salts, racemic mixtures and enantiomers thereof.

Another aspect of the present invention includes compounds of Formula (I.3) wherein R_1 is -NH(R_6), -tetrahydropyrimidinyl(R_8) or -tetrahydro-1,8-naphthyridinyl(R_8); and, all other variables are as previously defined.

Aspects of the present invention include a compound of Formula (I) wherein the compound is a compound of Formula (I.4):



Formula (I.4)

wherein R_2 and Z are as previously defined; and, further, R_2 is selected from the group consisting of -2-benzofuranyl, -3-benzofuranyl, -4-benzofuranyl, -5-benzofuranyl, -6-benzofuranyl, -7-benzofuranyl, -benzo[*b*]thien-2-yl, -benzo[*b*]thien-3-yl, -benzo[*b*]thien-4-yl, -benzo[*b*]thien-5-yl, -benzo[*b*]thien-6-yl, -benzo[*b*]thien-7-yl, -1*H*-indol-2-yl, -1*H*-indol-3-yl, -1*H*-indol-4-yl, -1*H*-indol-5-yl, -1*H*-indol-6-yl, -1*H*-indol-7-yl, -2-benzoxazolyl, -4-benzoxazolyl, -5-benzoxazolyl,

-6-benzoxazolyl, -7-benzoxazolyl, -2-benzothiazolyl, -3-benzothiazolyl, -4-benzothiazolyl, -5-benzothiazolyl, -6-benzothiazolyl, -7-benzothiazolyl, -1_H_-benzimidazolyl-2-yl, -1_H_-benzimidazolyl-4-yl, -1_H_-benzimidazolyl-5-yl, -1_H_-benzimidazolyl-6-yl, -1_H_-benzimidazolyl-7-yl, -2-quinolinyl, -3-quinolinyl, -4-quinolinyl, -5-quinolinyl, -6-quinolinyl, -7-quinolinyl, -8-quinolinyl, -2_H_-1-benzopyran-2-yl, -2_H_-1-benzopyran-3-yl, -2_H_-1-benzopyran-4-yl, -2_H_-1-benzopyran-5-yl, -2_H_-1-benzopyran-6-yl, -2_H_-1-benzopyran-7-yl, -2_H_-1-benzopyran-8-yl, -4_H_-1-benzopyran-2-yl, -4_H_-1-benzopyran-3-yl, -4_H_-1-benzopyran-4-yl, -4_H_-1-benzopyran-5-yl, -4_H_-1-benzopyran-6-yl, -4_H_-1-benzopyran-7-yl, -4_H_-1-benzopyran-8-yl, -1_H_-2-benzopyran-1-yl, -1_H_-2-benzopyran-3-yl, -1_H_-2-benzopyran-3-yl, -1_H_-2-benzopyran-5-yl, -1_H_-2-benzopyran-6-yl, -1_H_-2-benzopyran-7-yl, -1_H_-2-benzopyran-8-yl, -1,2,3,4-tetrahydro-1-naphthalenyl, -1,2,3,4-tetrahydro-2-naphthalenyl, -1,2,3,4-tetrahydro-5-naphthalenyl, -1,2,3,4-tetrahydro-6-naphthalenyl, -2,3-dihydro-2-benzofuranyl, -2,3-dihydro-3-benzofuranyl, -2,3-dihydro-4-benzofuranyl, -2,3-dihydro-5-benzofuranyl, -2,3-dihydro-6-benzofuranyl, -2,3-dihydro-7-benzofuranyl, -2,3-dihydrobenzo[_b_]thien-2-yl, -2,3-dihydrobenzo[_b_]thien-3-yl, -2,3-dihydrobenzo[_b_]thien-4-yl, -2,3-dihydrobenzo[_b_]thien-5-yl, -2,3-dihydrobenzo[_b_]thien-6-yl, -2,3-dihydrobenzo[_b_]thien-7-yl, -2,3-dihydro-1_H_-indol-2-yl, -2,3-dihydro-1_H_-indol-3-yl, -2,3-dihydro-1_H_-indol-4-yl, -2,3-dihydro-1_H_-indol-5-yl, -2,3-dihydro-1_H_-indol-6-yl, -2,3-dihydro-1_H_-indol-7-yl, -2,3-dihydro-2-benzoxazolyl, -2,3-dihydro-4-benzoxazolyl, -2,3-dihydro-5-benzoxazolyl, -2,3-dihydro-6-benzoxazolyl, -2,3-dihydro-7-benzoxazolyl, -2,3-dihydro-1_H_-benzimidazol-2-yl, -2,3-dihydro-1_H_-benzimidazol-4-yl, -2,3-dihydro-1_H_-benzimidazol-5-yl, -2,3-dihydro-1_H_-benzimidazol-6-yl, -2,3-dihydro-1_H_-benzimidazol-7-yl, -3,4-dihydro-1(2_H_)-quinolinyl, -1,2,3,4-tetrahydro-2-quinolinyl, -1,2,3,4-tetrahydro-3-quinolinyl, -1,2,3,4-tetrahydro-4-quinolinyl, -1,2,3,4-tetrahydro-5-quinolinyl, -1,2,3,4-tetrahydro-6-quinolinyl, -1,2,3,4-tetrahydro-7-quinolinyl, -1,2,3,4-tetrahydro-8-quinolinyl,

-3,4-dihydro-2*H*-1-benzopyran-2-yl, -3,4-dihydro-2*H*-1-benzopyran-3-yl, -3,4-dihydro-2*H*-1-benzopyran-4-yl, -3,4-dihydro-2*H*-1-benzopyran-5-yl, -3,4-dihydro-2*H*-1-benzopyran-6-yl, -3,4-dihydro-2*H*-1-benzopyran-7-yl, -3,4-dihydro-2*H*-1-benzopyran-8-yl, -3,4-dihydro-4*H*-1-benzopyran-2-yl, -3,4-dihydro-4*H*-1-benzopyran-3-yl, -3,4-dihydro-4*H*-1-benzopyran-4-yl, -3,4-dihydro-4*H*-1-benzopyran-5-yl, -3,4-dihydro-4*H*-1-benzopyran-6-yl, -3,4-dihydro-4*H*-1-benzopyran-7-yl, -3,4-dihydro-4*H*-1-benzopyran-8-yl, -3,4-dihydro-1*H*-2-benzopyran-2-yl, -3,4-dihydro-1*H*-2-benzopyran-3-yl, -3,4-dihydro-1*H*-2-benzopyran-4-yl, -3,4-dihydro-1*H*-2-benzopyran-5-yl, -3,4-dihydro-1*H*-2-benzopyran-6-yl, -3,4-dihydro-1*H*-2-benzopyran-7-yl and -3,4-dihydro-1*H*-2-benzopyran-8-yl optionally substituted when allowed by available valences with up to 7 substituents independently selected from methyl when attached to a nitrogen atom; and, independently selected from methyl, methoxy or fluoro when attached to a carbon atom;

Z is selected from the group consisting of hydroxy, $-NH_2$, $-NH-C_{1-8}$alkyl, $-N(C_{1-8}alkyl)_2$, $-O-C_{1-8}$alkyl, $-O-C_{1-8}$alkyl-OH, $-O-C_{1-8}$alkylC_{1-8}alkoxy, $-O-C_{1-8}$alkylcarbonylC_{1-8}alkyl, $-O-C_{1-8}$alkyl-CO_2H, $-O-C_{1-8}$alkyl-C(O)O-C_{1-8}alkyl, $-O-C_{1-8}$alkyl-O-C(O)C_{1-8}alkyl, $-O-C_{1-8}$alkyl-NH_2, $-O-C_{1-8}$alkyl-NH-C_{1-8}alkyl, $-O-C_{1-8}$alkyl-$N(C_{1-8}alkyl)_2$, $-O-C_{1-8}$alkylamide, $-O-C_{1-8}$alkyl-C(O)-NH-C_{1-8}alkyl, $-O-C_{1-8}$alkyl-C(O)-$N(C_{1-8}alkyl)_2$ and $-NHC(O)C_{1-8}$alkyl;

pharmaceutically acceptable salts, racemic mixtures and enantiomers thereof.

The compounds of the present invention may also be present in the form of pharmaceutically acceptable salts. For use in medicine, the salts of the compounds of this invention refer to non-toxic "pharmaceutically acceptable salts" (*Ref. International J. Pharm.,* **1986**, *33,* 201-217; *J. Pharm.Sci.,* **1977** (Jan), *66, 1,* 1). Other salts may, however, be useful in the preparation of compounds according to this invention or of their pharmaceutically acceptable salts. Representative organic or inorganic acids include, but are not limited to, hydrochloric, hydrobromic, hydriodic, perchloric, sulfuric, nitric, phosphoric, acetic, propionic, glycolic, lactic, succinic, maleic, fumaric,

malic, tartaric, citric, benzoic, mandelic, methanesulfonic, hydroxyethanesulfonic, benzenesulfonic, oxalic, pamoic, 2-naphthalenesulfonic, p-toluenesulfonic, cyclohexanesulfamic, salicylic, saccharinic or trifluoroacetic acid. Representative organic or inorganic bases include, but are not limited to, basic or cationic salts such as benzathine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine, procaine, aluminum, calcium, lithium, magnesium, potassium, sodium and zinc.

The present invention includes within its scope prodrugs of the compounds of this invention. In general, such prodrugs will be functional derivatives of the compounds which are readily convertible *in vivo* into the required compound. Thus, in the methods of treatment of the present invention, the term "administering" shall encompass the treatment of the various disorders described with the compound specifically disclosed or with a compound which may not be specifically disclosed, but which converts to the specified compound *in vivo* after administration to the subject. Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in "Design of Prodrugs", ed. H. Bundgaard, Elsevier, 1985.

Where the compounds according to this invention have at least one chiral center, they may accordingly exist as enantiomers. Where the compounds possess two or more chiral centers, they may additionally exist as diastereomers. Where the processes for the preparation of the compounds according to the invention give rise to mixtures of stereoisomers, these isomers may be separated by conventional techniques such as preparative chromatography. The compounds may be prepared in racemic form or as individual enantiomers or diasteromers by either stereospecific synthesis or by resolution. The compounds may be resolved into their component enantiomers or diasteromers by standard techniques. It is to be understood that all stereoisomers, racemic mixtures, diastereomers and enantiomers thereof are encompassed within the scope of the present invention.

During any of the processes for preparation of the compounds of the present invention, it may be necessary and/or desirable to protect sensitive or reactive groups on

any of the molecules concerned. This may be achieved by means of conventional protecting groups, such as those described in Protective Groups in Organic Chemistry, ed. J.F.W. McOmie, Plenum Press, 1973; and T.W. Greene & P.G.M. Wuts, Protective Groups in Organic Synthesis, John Wiley & Sons, 1991. The protecting groups may be removed at a convenient subsequent stage using methods known in the art.

Furthermore, some of the crystalline forms for the compounds may exist as polymorphs and as such are intended to be included in the present invention. In addition, some of the compounds may form solvates with water (i.e., hydrates) or common organic solvents and such solvates are also intended to be encompassed within the scope of this invention.

As used herein, the following underlined terms are intended to have the following meanings:

The term "$C_{a\text{-}b}$" (where *a* and *b* are integers referring to a designated number of carbon atoms) refers to an alkyl, alkenyl, alkynyl, alkoxy or cycloalkyl radical or to the alkyl portion of a radical in which alkyl appears as the prefix root containing from *a* to *b* carbon atoms inclusive. For example, $C_{1\text{-}3}$ denotes a radical containing 1, 2 or 3 carbon atoms.

The term "alkyl" refers to an optionally substituted saturated or partially unsaturated, branched, straight-chain or cyclic monovalent hydrocarbon radicals derived by the removal of one hydrogen atom from a single carbon atom of an alkane molecule, thus forming the point of attachment. The term "alkenyl" refers to an optionally substituted partially unsaturated branched or straight-chain monovalent hydrocarbon radical having at least one carbon-carbon double bond and derived by the removal of one hydrogen atom from a single carbon atom of an alkene molecule, thus forming the point of attachment. The radical may be in either the *cis* or *trans* conformation about the double bond(s). The term "alkynyl" refers to an optionally substituted partially unsaturated branched or straight-chain monovalent hydrocarbon radical having at least one carbon-carbon triple bond and derived by the removal of one

hydrogen atom from a single carbon atom of an alkyne molecule, thus forming the point of attachment. The term “alkoxy” refers to an optionally substituted saturated or partially unsaturated, branched, straight-chain monovalent hydrocarbon radical derived by the removal of the hydrogen atom from the single oxygen atom of an alkane, alkene or alkyne molecule, thus forming the point of attachment. An alkyl alkenyl, alkynyl or alkoxy radical is optionally substituted within the radical or on a terminal carbon atom (for a chain) with that amount of substituents allowed by available saturated valences.

The term “$-C_{1-8}$alkyl(R_x)” (where x is an integer referring to a designated substitutent group) refers to an R_x substituent group which may be substituted within an alykl chain, on a terminal carbon atom and may be similarly substituted on an alkenyl, alkynyl or alkoxy radical with a designated amount of substituents where allowed by available chemical bond valences. The term “$-C_{0-8}$alkyl(R_x)” refers to an R_x substituent group which may also be directly substituted on a pointof attachment without an alkyl linking group (wherein C_0 is a placeholder for the R_x substituent with a direct bond to the point of attachment).

The term “cycloalkyl” refers to saturated or partially unsaturated cyclic monovalent hydrocarbon radical consistent with the definitions of alkyl, alkanyl, alkenyl and alkynyl. Specifically included within the definition of cycloalkyl are fused polycyclic ring systems in which one or more rings are aromatic and one or more rings are saturated or partially unsaturated (it being understood that the radical may also occur on the aromatic ring). For example, the cycloalkyl groups are saturated or partially unsaturated or monocyclic alkyl radicals of from 3-8 carbon atoms (derived from a molecule such as cyclopropane, cyclobutane, cyclopentane, cyclohexane or cycloheptane); saturated or partially unsaturated fused or benzofused cyclic alkyl radicals of from 9 to 12 carbon atoms; or, saturated or partially unsaturated fused or benzofused tricyclic or polycyclic alkyl radicals of from 13 to 20 carbon atoms.

The term “heterocyclyl” refers to a saturated or partially unsaturated cyclic alkyl radical in which one or more carbon atoms are independently replaced with the same or different heteroatom. Specifically included within the definition of heterocyclyl are

fused polycyclic ring systems in which one or more rings are aromatic and one or more rings are saturated or partially unsaturated (it being understood that the radical may also occur on the aromatic ring). Typical heteroatoms to replace the carbon atom(s) include, but are not limited to, N, O, S and the like. For example, the heterocyclyl group is a saturated or partially unsaturated five membered monocyclic alkyl ring of which at least one member is replaced by a N, O or S atom and which optionally contains one additional O atom replacing an additional member of the alkyl ring or one additional N atom replacing a member of the alkyl ring; a saturated or partially unsaturated six membered monocyclic alkyl ring of which one, two or three members of the alkyl ring are replaced by a N atom and optionally one member of the alkyl ring is replaced by a O or S atom or two members of the alkyl ring are replaced by O or S atoms; a saturated or partially unsaturated 5-6 membered heterocylic ring as previously defined fused to a heteroaryl as hereinafter defined; a saturated, partially unsaturated or benzofused nine or 10 membered bicyclic alkyl wherein at least one member of the ring is replaced by N, O, or S atom and which optionally one or two additional members of the bicyclic alkyl are replaced by N, O or S atoms; or, a saturated, partially unsaturated or benzofused 11 to 20 membered polycyclic alkyl of which at least one member is replaced by a N, O or S atom and which optionally one, two or three additional members of the polycyclic alkyl are replaced by N atoms. Examples of saturated or partially unsaturated heterocyclyl radicals include, but are not limited to, 2-pyrrolinyl, 3-pyrrolinyl, pyrrolidinyl, 1,3-dioxolanyl, 2-imidazolinyl, imidazolidinyl, dihydroimdazolyl, 2-pyrazolinyl, pyrazolidinyl, piperidinyl, morpholinyl, tetrahydropyrimidinyl, piperazinyl, dihydro-1H-pyrrolo[2,3-b]pyridinyl, tetrahydro-1, 8-naphthyridinyl, tetrahydro-1H-azepino[2,3-b]pyridinyl, 1,3-benzodioxol-5-yl, 1,2,3,4-tetrahydro-3-quinolinyl or dihydrobenzofuranyl.

The term "aryl" refers to a monovalent aromatic hydrocarbon radical derived by the removal of one hydrogen atom from a single carbon atom of an aromatic ring system, thus forming the point of attachment for the radical. For example, the aryl group is derived from an unsaturated aromatic monocyclic ring system containing 5 to 6 carbon atoms (such as phenyl, derived from benzene); an unsaturated aromatic bicyclic ring system containing 9 to 10 carbon atoms (such as naphthyl, derived from

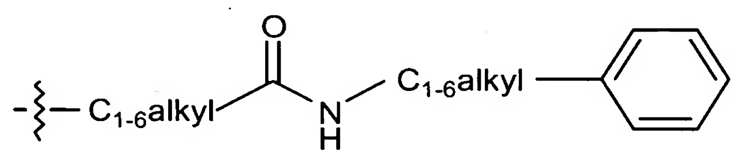
naphthalene); or, an unsaturated aromatic tricyclic ring system containing 13 to 14 hydrogen carbon atoms (such as anthracenyl, derived from anthracene). The term "aromatic ring system" refers to an unsaturated cyclic or polycyclic ring system having an "aromatic" conjugated π electron system. Specifically excluded from the definition of aryl are fused ring systems in which one or more rings are saturated or partially unsaturated. Typical aryl groups include, but are not limited to, anthracenyl, naphthalenyl, azulenyl, benzenyl and the like

The term "heteroaryl" refers to a monovalent heteroaromatic radical derived by the removal of one hydrogen atom from a single atom of a heteroaromatic ring system, thus forming the point of attachment for the radical. The term "heteroaromatic ring system" refers to an aromatic ring system in which one or more carbon atoms are each independently replaced with a heteroatom. Typical heteratoms to replace the carbon atoms include, but are not limited to, N, O, S, and the like. Specifically excluded from the definition of heteroaromatic ring system are fused ring systems in which one or more rings are saturated or partially unsaturated. For example, the heteroaryl group is derived from a heteroaromatic monocyclic ring system containing five members of which at least one member is a N, O or S atom and which optionally contains one, two or three additional N atoms; a heteroaromatic monocyclic ring system having six members of which one, two or three members are an N atom; a heteroaromatic fused bicyclic ring system having nine members of which at least one member is a N, O or S atom and which optionally contains one, two or three additional N atoms; a heteroaromatic fused bicyclic ring system having ten members of which one, two or three members are a N atom; a heteroaromatic fused tricyclic ring system containing 13 or 14 members of which at least one member is a N, O or S atom and which optionally contains one, two or three additional N atoms; or, a heteroaromatic fused polycyclic ring system containing 15 to 20 members of which at least one member is a N, O or S atom and which optionally contains one, two or three additional N atoms. Typical heteroaryls include, but are not limited to, cinnolinyl, furanyl, imidazolyl, indazolyl, indolyl, indolinyl, indolizinyl, isobenzofuranyl, isoquinolinyl, isothiazolyl, isoxazolyl, naphthyridinyl, oxazolyl, phenanthridinyl, phenanthrolinyl, purinyl, pyranyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridinyl, pyrimidinyl, pyrrolyl, quinazolinyl,

quinolinyl, quinoxalinyl, tetrazole, thiadiazole, thiazole, thiophene, triazole and the like.

The term “independently” means that when a group is substituted with more than one substituent that the substituents may be the same or different. The term “dependently” means that the substituents are specified in an indicated combination of structure variables.

Under standard nomenclature rules used throughout this disclosure, the terminal portion of the designated side chain is described first followed by the adjacent functionality toward the point of attachment. Thus, for example, a “phenylC_{1-6}alkylamidoC_{1-6}alkyl” substituent refers to a group of the formula:



A substituent’s point of attachment may also be indicated by a dashed line to indicate the point(s) of attachment, followed by the adjacent functionality and ending with the terminal functionality such as, for example, _-(C_{1-6})alkyl-carbonyl-NH-(C_{1-6})alkyl-phenyl.

It is intended that the definition of any substituent or variable at a particular location in a molecule be independent of its definitions elsewhere in that molecule. It is understood that substituents and substitution patterns on the compounds of this invention can be selected by one of ordinary skill in the art to provide compounds that are chemically stable and that can be readily synthesized by techniques known in the art as well as those methods set forth herein.

Integrins are a widely expressed family of calcium or magnesium dependent α or β heterodimeric cell surface receptors, which bind to extracellular matrix adhesive proteins such as fibrinogen, fibronectin, vitronectin and osteopontin. The integrin receptors are transmembrane glycoproteins (GP’s) known for their large extracellular

domains and are classified by at least 8 known β subunits and 14 α subunits (S. A. Mousa, et al., *Emerging Theraupeutic Targets,* **2000**, *4,* (2), 143-153).

For example, the β1 subfamily has the largest number of integrins wherein the various α subunits associate with various β subunits: β3, β5, β6 and β8 (S. A. Mousa, et al., *Emerging Theraupeutic Targets,* **2000**, *4,* (2), 144-147). Some of the disease states that have a strong αvβ3, αvβ5 and αIIbβ3 (also referred to as GPIIb/IIIa) integrin component in their etiologies are unstable angina, thromboembolic disorders or atherosclerosis (GPIIb/IIIa); thrombosis or restenosis (GPIIb/IIIa or αvβ3); restenosis (dual αvβ3/GPIIb/IIIa); rheumatoid arthritis, vascular disorders or osteoporosis (αvβ3); tumor angiogenesis, tumor metastasis, tumor growth, multiple sclerosis, neurological disorders, asthma, vascular injury or diabetic retinopathy (αvβ3 or αvβ5); and, angiogenesis (dual αvβ3/αvβ5) (S. A. Mousa, et al., *Emerging Theraupeutic Targets,* **2000**, *4,* (2), 148-149; W. H. Miller, et al., *Drug Discovery Today* **2000**, *5* (9), 397-407; and, S. A. Mousa, et al., *Exp. Opin. Ther. Patents,* **1999**, *9* (9), 1237-1248). The β3 subunit has received significant attention in recent drug discovery efforts. (W. J. Hoekstra, *Current Medicinal Chemistry* **1998**, *5*, 195). Antibodies and/or low-molecular weight compound antagonists of αvβ3 have shown efficacy in animal models (J. Samanen, *Current Pharmaceutical Design* **1997**, *3*, 545) and, thereby, offer promise as medicinal agents.

Integrin antagonists have typically been designed after the bioactive arginine-glycine-aspartate (RGD) conformation of peptides derived from the primary ligand vitronectin. The RGD motif is the general cell attachment sequence of many extracellular matrix, blood and cell surface proteins, as half of the approximately 20 known integrins bind the RGD-containing adhesion ligands. To discover RGD peptides with integrin selectivity, peptides with both restricted conformations and alterations of flanking residues have been studied. In particular, the structural requirements for interaction of the RGD sequence with GPIIb/IIIa and the inhibitory potential of a series of nonpeptidic mimetics on platelet aggregation and interactions with the extracellular matrix have been described (D. Varon, et al., *Thromb. Haemostasis*, **1993**, *70(6)*, 1030-1036). Iterative synthesis of cyclic and alicyclic

peptides and computer modelling have provided potent, selective agents as a platform for nonpeptide αv (as in αvβ3) integrin antagonist design.

Integrin antagonists have been implicated as useful for inhibiting bone resorption (S.B. Rodan and G.A. Rodan, Integrin Function In Osteoclasts, *Journal of Endocrinology*, **1997**, 154: S47-S56). In vertebrates, bone resorption is mediated by the action of cells known as osteoclasts, large multinucleated cells of up to about 400 mm in diameter that resorb mineralized tissue, chiefly calcium carbonate and calcium phosphate. Osteoclasts are actively motile cells that migrate along the surface of bone and can bind to bone, secrete necessary acids and proteases, thereby causing the actual resorption of mineralized tissue from the bone. More specifically, osteoclasts are believed to exist in at least two physiological states, namely, the secretory state and the migratory or motile state. In the secretory state, osteoclasts are flat, attach to the bone matrix via a tight attachment zone (sealing zone), become highly polarized, form a ruffled border and secrete lysosomal enzymes and protons to resorb bone. The adhesion of osteoclasts to bone surfaces is an important initial step in bone resorption. In the migratory or motile state, osteoclasts migrate across bone matrix and do not take part in resorption until they again attach to bone.

Integrins are involved in osteoclast attachment, activation and migration. The most abundant integrin receptor on osteoclasts (e.g., on rat, chicken, mouse and human osteoclasts) is the αvβ3 integrin receptor, which is thought to interact in bone with matrix proteins that contain the RGD sequence. Antibodies to αvβ3 block bone resorption in vitro, indicating that this integrin plays a key role in the resorptive process. There is increasing evidence to suggest that αvβ3 ligands can be used effectively to inhibit osteoclast mediated bone resorption in vivo in mammals.

The current major bone diseases of public concern are osteoporosis, hypercalcemia of malignancy, osteopenia due to bone metastases, periodontal disease, hyperparathyroidism, periarticular erosions in rheumatoid arthritis, Paget's disease, immobilization-induced osteopenia and glucocorticoid-induced osteoporosis. All of these conditions are characterized by bone loss, resulting from an imbalance between

bone resorption, i.e. breakdown and bone formation, which continues throughout life at the rate of about 14% per year on the average. However, the rate of bone turnover differs from site to site; for example, it is higher in the trabecular bone of the vertebrae and the alveolar bone in the jaws than in the cortices of the long bones. The potential for bone loss is directly related to turnover and can amount to over 5% per year in vertebrae immediately following menopause, a condition that leads to increased fracture risk.

In the United States, there are currently about 20 million people with detectable fractures of the vertebrae due to osteoporosis. In addition, there are about 250,000 hip fractures per year attributed to osteoporosis. This clinical situation is associated with a 12% mortality rate within the first two years, while 30% of the patients require nursing home care after the fracture. Individuals suffering from all the conditions listed above would benefit from treatment with agents that inhibit bone resorption.

Additionally, αvβ3 ligands have been found to be useful in treating and/or inhibiting restenosis (i.e. recurrence of stenosis after corrective surgery on the heart valve), atherosclerosis, diabetic retinopathy, macular degeneration and angiogenesis (i.e. formation of new blood vessels) and inhibiting viral disease.

Moreover, it has been postulated that the growth of tumors depends on an adequate blood supply, which in turn is dependent on the growth of new vessels into the tumor; thus, inhibition of angiogenesis can cause tumor regression in animal models (Harrison's Principles of Internal Medicine, **1991**, 12th ed.). Therefore, αvβ3 antagonists, which inhibit angiogenesis can be useful in the treatment of cancer by inhibiting tumor growth (Brooks et al., *Cell*, **1994**, 79, 1157-1164). Evidence has also been presented suggesting that angiogenesis is a central factor in the initiation and persistence of arthritic disease and that the vascular integrin αvβ3 may be a preferred target in inflammatory arthritis. Therefore, αvβ3 antagonists that inhibit angiogenesis may represent a novel therapeutic approach to the treatment of arthritic disease, such as rheumatoid arthritis (C.M. Storgard, et al., Decreased Angiogenesis and Arthritic

Disease in Rabbits Treated with an $\alpha v\beta 3$ Antagonist, *J. Clin. Invest.*, **1999**, 103, 47-54).

Inhibition of the $\alpha v\beta 5$ integrin receptor can also prevent neovascularization. A monoclonal antibody for $\alpha v\beta 5$ has been shown to inhibit VEGF-induced angiogenesis in rabbit cornea and the chick chorioallantoic membrane model (M.C. Friedlander, et al., *Science*, **1995**, 270, 1500-1502). Thus, $\alpha v\beta 5$ antagonists are useful for treating and preventing macular degeneration, diabetic retinopathy, cancer and metastatic tumor growth.

Inhibition of αv integrin receptors can also prevent angiogenesis and inflammation by acting as antagonists of other β subunits, such as $\alpha v\beta 6$ and $\alpha v\beta 8$ (Melpo Christofidou-Solomidou, et al., Expression and Function of Endothelial Cell on Integrin Receptors in Wound-Induced Human Angiogenesis in Human Skin/SCID 25 Mice Chimeras, *American Journal of Pathology,* **1997**, 151, 975-83; and, Xiao-Zhu Huang, et al., Inactivation of the Integrin $\beta 6$ Subunit Gene Reveals a Role of Epithelial Integrins in Regulating Inflamnation in the Lungs and Skin, *Journal of Cell Biology,* **1996**, 133, 921-28).

An antagonist to the αv integrin can act to inhibit or minimize adhesions that result from either wounding or surgical adhesions. Post-surgical adhesions result as an anomaly of the wound healing process. Cell adhesion and the migration of fibroblasts are major players in this process. Trauma caused by the wounding, a surgical procedure, normal tissue manipulation in surgery, or bleeding during a surgical procedure can act to disrupt the peritoneum and expose the underlying stroma leading to the release of inflammatory mediators and an increase in capillary permeability. Inflammatory cells are subsequently liberated and the formation of a fibrin clot ensues. Adhesions are formed and intensify as fibroblasts and inflammatory cells continue to infiltrate this extracellular matrix rich in fibrin. The extracellular matrix is composed of adhesive proteins which act as ligands for the αv integrin. To inhibit post-surgical adhesion development, application of an αv antagonist could be parenteral, subcutaneous, intravenous, oral, topical or transdermal. The αv integrin antagonist can

be administered before, during or after a surgical procedure. When administered during a surgical procedure the antagonists can be administered by aerosol, in a pad, gel, film, sponge, solution, suspension or similar suitable pharmaceutically acceptable carrier to the area in which the surgery is performed.

An aspect of the invention is a composition or medicament comprising a pharmaceutically appropriate carrier and any of the compounds of the present invention. Illustrative of the invention is a composition or medicament made by mixing an instant compound and a pharmaceutically appropriate carrier. Another illustration of the invention is a process for making a composition or medicament comprising mixing any of the compounds described above and a pharmaceutically appropriate carrier. Further illustrative of the present invention are compositions or medicaments comprising one or more compounds of this invention in association with a pharmaceutically appropriate carrier.

As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combinations of the specified ingredients in the specified amounts for treating or ameliorating an αv integrin mediated disorder or for use as a medicament.

The compounds of the present invention are αv integrin inhibitors useful for treating or ameliorating an αv integrin mediated disorder. An aspect of the invention includes compounds that are selective inhibitors of an αv integrin receptor, or subtype thereof. In another aspect of the invention, the inhibitor is independently selective to the $\alpha v\beta 3$ integrin receptor or the $\alpha v\beta 5$ integrin receptor. An aspect of the invention also includes compounds that are inhibitors of a combination of αv integrin receptors, or subtypes thereof. In another aspect of the invention, the compound inhibitor simultaneously antagonizes both the $\alpha v\beta 3$ integrin and the $\alpha v\beta 5$ integrin receptor subtypes.

An aspect of the present invention includes a method for treating or

ameliorating an αv integrin mediated disorder in a subject in need thereof comprising administering to the subject a therapeutically effective amount of a compound of Formula (I) or composition thereof.

The term "therapeutically effective amount" or "effective amount," as used herein, means that amount of active compound or pharmaceutical agent that elicits the biological or medicinal response in a tissue system, animal or human, that is being sought by a researcher, veterinarian, medical doctor, or other clinician, which includes alleviation of the symptoms of the disease or disorder being treated.

An aspect of the present invention includes a prophylactic method for preventing an αv integrin mediated disorder in a subject in need thereof comprising administering to the subject a prophylactically effective amount of a compound of Formula (I) or composition thereof.

Another aspect of the present invention includes the preparation of a medicament comprising a therapeutically effective amount of a compound of Formula (I) for use in preventing, treating or ameliorating an αv integrin mediated disorder in a subject in need thereof.

The term "administering" is to be interpreted in accordance with the methods of the present invention whereby an individual compound of the present invention or a composition thereof can be therapeutically administered separately at different times during the course of therapy or concurrently in divided or single combination forms. Prophylactic administration can occur prior to the manifestation of symptoms characteristic of an αv integrin mediated disease or disorder such that the disease or disorder is prevented or, alternatively, delayed in its progression. The instant invention is therefore to be understood as embracing all such regimes of simultaneous or alternating therapeutic or prophylatic treatment.

The term "subject" as used herein, refers to an animal, preferably a mammal, most preferably a human, which has been the object of treatment, observation or

experiment and is at risk of (or susceptible to) developing a disease or disorder or having a disease or disorder related to expression of an αv integrin, or subtype thereof.

The term "αv integrin mediated disorder" refers to disorders and diseases associated with pathological unregulated or disregulated cell proliferation resulting from expression of an αv integrin, or subtype thereof.

The term "unregulated" refers to a breakdown in the process of regulating cell proliferation, as in a tumor cell. The term "disregulated" refers to inappropriate cell growth as a result of pathogenesis. The term "subtype" refers to a particular αv integrin receptor selected from those receptors making up the class of αv integrins, such as an αvβ3 integrin receptor or an αvβ5 integrin receptor.

The term "disorders and diseases associated with unregulated or disregulated cell proliferation" refers to disorders wherein cell proliferation by one or more subset of cells in a multicellular organism results in harm (such as discomfort or decreased life expectancy) to the organism. Such disorders can occur in different types of animals and humans and include, and are not limited to, cancers, cancer-associated pathologies, atherosclerosis, transplantation-induced vasculopathies, neointima formation, papilloma, lung fibrosis, pulmonary fibrosis, glomerulonephritis, glomerulosclerosis, congenital multicystic renal dysplasia, kidney fibrosis, diabetic retinopathy, macular degeneration, psoriasis, osteoporosis, bone resorption, inflammatory arthritis, rheumatoid arthritis, restenosis or adhesions.

The term "cancers" refers to, and is not limited to, glioma cancers, lung cancers, breast cancers, colorectal cancers, prostate cancers, gastric cancers, esophageal cancers, leukemias, melanomas, basal cell carcinomas and lymphomas. The term "cancer-associated pathologies" refers to, and is not limited to, unregulated or disregulated cell proliferation, tumor growth, tumor vascularization, angiopathy and angiogenesis. The term "angiogenesis" refers to, and is not limited to, unregulated or disregulated proliferation of new vascular tissue including, but not limited to, endothelial cells, vascular smooth muscle cells, pericytes and fibroblasts. The term "osteoporosis" refers

to, and is not limited to, formation or activity of osteoclasts resulting in bone resorption. The term “restenosis” refers to, and is not limited to, in-stent stenosis and vascular graft restenosis.

The term "αv integrin expression" refers to expression of an αv integrin, or subtype thereof, which leads to unregulated or disregulated cell proliferation:

1. by cells which do not normally express an αv integrin, or subtype thereof,
2. by neoplastic cells,
3. in response to stimulation by a growth factor, hypoxia, neoplasia or a disease process,
4. as a result of mutations which lead to constitutive expression of an αv integrin, or subtype thereof.

The expression of an αv integrin, or subtype thereof, includes selective expression of an αv integrin or subtype thereof, selective expression of the αvβ3 integrin or the αvβ5 integrin subtypes, expression of multiple αv integrin subtypes or simultaneous expression of the αvβ3 integrin and the αvβ5 integrin subtypes. Detecting the expression of an αv integrin, or subtype thereof, in inappropriate or abnormal levels is determined by procedures well known in the art.

Another aspect of the present invention includes a method for treating or ameliorating a selective αvβ3 integrin mediated disorder in a subject in need thereof comprising administering to the subject a therapeutically effective amount of a compound of Formula (I) or composition thereof.

Another aspect of the present invention includes a method for treating or ameliorating a selective αvβ5 integrin mediated disorder in a subject in need thereof comprising administering to the subject a therapeutically effective amount of a compound of Formula (I) or composition thereof.

Another aspect of the present invention includes a method for treating or ameliorating a disorder simultaneously mediated by an αvβ3 and αvβ5 integrin in a

subject in need thereof comprising administering to the subject a therapeutically effective amount of a compound of Formula (I) or composition thereof.

An aspect of the present invention includes a method for inhibiting αv integrin mediated neoplastic activity comprising administering to a neoplasm or to the microenvironment around the neoplasm an effective amount of a compound of Formula (I) or composition thereof.

The term "neoplastic activity" refers to unregulated or disregulated cell proliferation and the process of angiogenesis or the formation of new vasculature supporting a neoplasm in the endothelial microenvironment around the neoplasm.

The term "neoplasm" refers to tumor cells are cells having unregulated or disregulated proliferation as a result of genetic instability or mutation and an endothelium wherein the endothelial cells have unregulated or disregulated proliferation as a result of a pathogenic condition. Within the scope of the present invention, a neoplasm is not required to express the αv integrin, or subtype thereof, by itself and is not limited to a primary tumor of origin but also to secondary tumors occurring as a result of metastasis of the primary tumor. The term "administering to a neoplasm" refers to administering a compound of Formula (I) or composition thereof to the surface of a neoplasm, to the surface of a neoplastic cell or to the endothelial microenvironment around a neoplasm.

The term "inhibiting αv integrin mediated neoplastic activity" includes attenuating a tumor's growth by limiting its blood supply and, further, preventing the formation of new supportive vasculature by preventing the process of angiogenesis.

An aspect of the present invention includes a method for treating or ameliorating a disease mediated by cells pathologically expressing an αv integrin, or subtype thereof.

The term "disease mediated by cells pathologically expressing an αv integrin"

refers to, and is not limited to, a disorders selected from cancers, cancer-associated pathologies, diabetic retinopathy, macular degeneration, osteoporosis, bone resorption, inflammatory arthritis, rheumatoid arthritis or restenosis.

An aspect of the present invention includes a method for sustained neoplasm regression in a subject in need thereof comprising administering to the subject an effective amount of a compound of Formula (I) or composition thereof; wherein the compound or composition thereof is conjugated with and delivers a therapeutic agent to to a neoplasm or to the microenvironment around the neoplasm; and, wherein the therapeutic agent induces apoptosis or attenuates unregulated or disregulated cell proliferation.

The terms "conjugated with" and "delivers a therapeutic agent" refers to a compound of Formula (I) or composition thereof bound to a therapeutic agent by a conjugation means known to those skilled in the art; wherein the compound or composition thereof acts as a targeting agent for antagonizing the αv integrin receptors of a neoplasm or the microenvironment thereof; and, wherein the conjugation means facilitates and selectively delivers the therapeutic agent to the neoplasm or the microenvironment thereof.

The term "therapeutic agent," including but not limited to Technetium^{99}, refers to imaging agents known to those skilled in the art.

An aspect of the present invention includes a method for use of a compound of Formula (I) or composition thereof advantageously co administered in one or more tumor or cell anti-proliferation therapies including chemotherapy, radiation therapy, gene therapy or immunotherapy for preventing, treating or ameliorating an αv integrin mediated disorder.

The combination therapy can include:

1. co-administration of a compound of Formula (I) or composition thereof and a chemotherapeutic agent for preventing, treating or ameliorating an αv integrin

mediated disorder,

2. sequential administration of a compound of Formula (I) or composition thereof and a chemotherapeutic agent for preventing, treating or ameliorating an αv integrin mediated disorder,
3. administration of a composition containing a compound of Formula (I) and a chemotherapeutic agent for preventing, treating or ameliorating an αv integrin mediated disorder, or,
4. simultaneous administration of a separate composition containing a compound of Formula (I) and a separate composition containing a chemotherapeutic agent for preventing, treating or ameliorating an αv integrin mediated disorder.

For example, the compounds of this invention are useful in combination therapies with at least one other chemotherapeutic agent for the treatment of a number of different cancers and advantageously appear to facilitate the use of a reduced dose of the chemotherapeutic agent that is recommended for a particular cancer or cell proliferation disorder. Therefore, it is contemplated that the compounds of this invention can be used in a treatment regime before the administration of a particular chemotherapeutic agent recommended for the treatment of a particular cancer, during administration of the chemotherapeutic agent or after treatment with a particular chemotherapeutic agent.

The term "chemotherapeutic agents" includes, and is not limited to, anti-angiogenic agents, anti-tumor agents, cytotoxic agents, inhibitors of cell proliferation and the like. The term "treating or ameliorating" includes, and is not limited to, facilitating the eradication of, inhibiting the progression of or promoting stasis of a malignancy. For example, an inhibitor compound of the present invention, acting as an anti-angiogenic agent can be administered in a dosing regimen with at least one other cytotoxic compound, such as a DNA alkylating agent.

Preferred anti-tumor agents are selected from the group consisting of cladribine (2-chloro-2'-deoxy-(beta)-D-adenosine), chlorambucil (4-(bis(2-chlorethyl)amino)benzenebutanoic acid), DTIC-Dome (5-(3,3-dimethyl-l-triazeno)-

imidazole-4-carboxamide), platinum chemotherapeutics and nonplatinum chemotherapeutics. Platinum containing anti-tumor agents include, and are not limited to, cisplatin (CDDP) (cis-dichlorodiamineplatinum). Non-platinum containing anti-tumor agents include, and are not limited to, adriamycin (doxorubicin), aminopterin, bleomycin, camptothecin, carminomycin, combretastatin(s), cyclophosphamide, cytosine arabinoside, dactinomycin, daunomycin, epirubicin, etoposide (VP-16), 5-fluorouracil (5FU), herceptin actinomycin-D, methotrexate, mitomycin C, tamoxifen, taxol, taxotere, thiotepa, vinblastine, vincristine, vinorelbine and derivatives and prodrugs thereof. Each anti-tumor agent is administered in a therapeutically effective amount, which varies based on the agent used, the type of malignancy to be treated or ameliorated and other conditions according to methods well known in the art.

As will be understood by those skilled in the art, the appropriate doses of chemotherapeutic agents will be generally around those already employed in clinical therapies wherein the chemotherapeutics are administered alone or in combination with other chemotherapeutics. By way of example only, agents such as cisplatin and other DNA alkylating are used widely to treat cancer. The efficacious dose of cisplatin used in clinical applications is about 20 mg/m^2 for 5 days every three weeks for a total of three courses. Cisplatin is not absorbed orally and must therefore be delivered via injection intravenously, subcutaneously, intratumorally or intraperitoneally. Further useful agents include compounds that interfere with DNA replication, mitosis and chromosomal segregation. Such chemotherapeutic agents include adriamycin (doxorubicin), etoposide, verapamil or podophyllotoxin and the like and are widely used in clinical settings for tumor treatment. These compounds are administered through bolus injections intravenously at doses ranging from about 25 to about 75 mg/m^2 at 21 day intervals (for adriamycin) or from about 35 to about 50 mg/m^2 (for etoposide) intravenously or at double the intravenous dose orally. Agents that disrupt the synthesis and fidelity of polynucleotide precursors such as 5-fluorouracil (5-FU) are preferentially used to target tumors. Although quite toxic, 5-FU is commonly used via intravenous administration with doses ranging from about 3 to about 15 mg/kg/day.

Another aspect of the present invention includes a method for administering a

compound of the present invention in combination with radiation therapy. As used herein, "radiation therapy" refers to a therapy that comprises exposing the subject in need thereof to radiation. Such therapy is known to those skilled in the art. The appropriate scheme of radiation therapy will be similar to those already employed in clinical therapies wherein the radiation therapy is used alone or in combination with other chemotherapeutics.

An aspect of the present invention includes a method for administering a compound of the present invention in combination with a gene therapy or for use of a compound of the present invention as a gene therapy means. The term "gene therapy" refers to a therapy targeting angiogenic endothelial cells or tumor tissue during tumor development. Gene therapy strategies include the restoration of defective cancer-inhibitory genes, cell transduction or transfection with antisense DNA (corresponding to genes coding for growth factors and their receptors) and the use of "suicide genes." The term "gene therapy means" refers to the use of a targeting vector comprising a combination of a cationic nanoparticle coupled to an αv-targeting ligand to influence blood vessel biology; whereby genes are selectively delivered to angiogenic blood vessels (as described in Hood, J.D., et al, Tumor Regression by Targeted Gene Delivery to the Neovasculature, *Science,* **2002**, 28 June, 296, 2404-2407).

Another aspect of the present invention includes a method for treating or ameliorating an αv integrin mediated neoplasm in a subject in need thereof comprising administering to the subject an effective amount of a gene therapy combination product comprising a compound of Formula (I) or composition thereof and a gene therapeutic agent; wherein the product is delivered or "seeded" directly to a neoplasm or the microenvironment thereof by antagonizing the αv integrin receptors of the neoplasm or microenvironment thereof.

The term "delivered or 'seeded' directly to a neoplasm" includes using a compound of Formula (I) or composition thereof as a gene therapy means whereby the compound or composition thereof functions as a targeting agent which directs the conjugate to its intended site of action (i.e., to neoplastic vascular endothelial cells or to

tumor cells). Because of the specific interaction of the αv integrin inhibitor as a targeting agent and its corresponding αv integrin receptor site, a compound of this invention can be administered with high local concentrations at or near a targeted αv integrin receptor, or subtype thereof, thus treating the αv integrin mediated disorder more effectively.

Another aspect of the present invention includes a method for administering a compound of the present invention in combination with an immunotherapy. As used herein, "immunotherapy" refers to a therapy targeted to a particular protein involved in tumor development via antibodies specific to such protein. For example, monoclonal antibodies against vascular endothelial growth factor have been used in treating cancers.

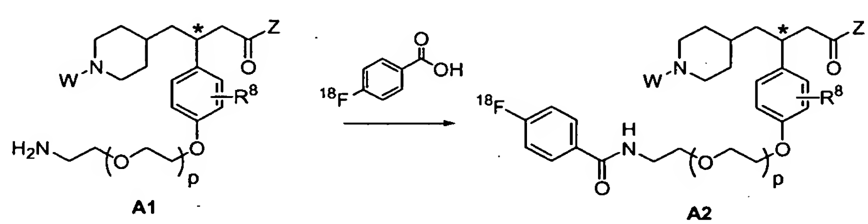
An aspect of the present invention includes a method for tumor imaging in a subject in need thereof comprising advantageously coadministering to the subject an effective amount of a compound of Formula (I) or composition thereof; wherein the compound or composition thereof is conjugated with and delivers a non-invasive tumor imaging agent to a tumor or to the microenvironment around the tumor.

The terms "conjugated with" and "delivers a non-invasive tumor imaging agent" refers to a compound of Formula (I) or composition thereof bound to an imaging agent by a conjugation means known to those skilled in the art; wherein the compound or composition thereof acts as a targeting agent for antagonizing the αv integrin receptors of a neoplasm or the microenvironment thereof; and, wherein the conjugation means facilitates and selectively delivers the imaging agent to the neoplasm or the microenvironment thereof (as described in PCT Application WO00/35887, WO00/35492, WO00/35488 or WO99/58162). The term "imaging agent," including but not limited to Technetium^{99}, refers to imaging agents known to those skilled in the art. The term "conjugation means," including but not limited to appending a compound to a linking group followed by conjugation with an imaging agent chelating group, refers to means known to those skilled in the art.

Since, cell adhesion molecules $\alpha_V\beta_3$ and $\alpha_V\beta_5$ play a pivotal role in certain disorders such as tumor angiogenesis and metastasis, and are only present at very low levels in normal non-proliferative tissue, $\alpha_V\beta_3$ and $\alpha_V\beta_5$ integrin receptor antagonists are potentially useful tools in non-invasive imaging and treatment. The ability to visualize and quantify integrin expression may provide a better understanding of disease progression such as tumor growth and efficiency of current methods of treatment.

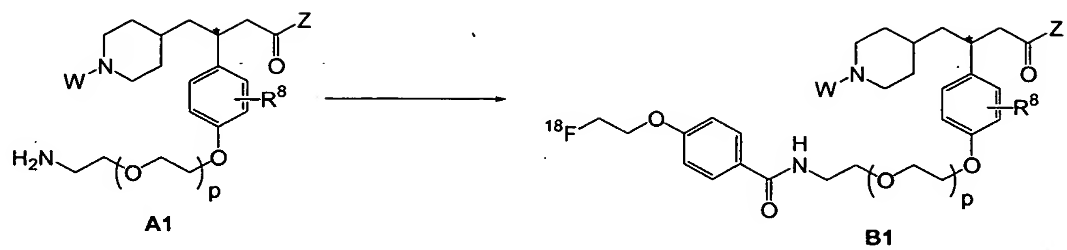
The $\alpha_V\beta_3$ and $\alpha_V\beta_5$ integrin receptor antagonists and more preferably the targeting ligands of the present invention may be labeled with radioactive elements such as ^{125}I, ^{18}F, ^{11}C, ^{64}Cu, and the like for use in imaging such as positron emission tomography (PET) imaging or for radioactive treatment of patients. The targeting ligands or affinity moieties described herein may be reacted with an appropriate functionalized radioactive reagents using conventional chemistry to provide a radiolabeled affinity moiety. For example radiopharmaceutical molecules may be synthesized using Compound **A1**, wherein R_{2A} comprises an aryl ring substituted with R_{15}, and said R_{15} is a PEG chain containing a reactive functional group such as amine, alcohol, or carboxylic acid. Compound **A1** may be coupled with a variety of activated radio-labeled molecules or other diagnostic agents that contain a reactive functional group, such as *p*-^{18}F-benzoic acid, to provide Compound **A2**.

Scheme A



Similarly, Compound **A1** may be coupled with *p*-hydroxybenzoic acid using reagents, protecting groups, and methods known to those skilled in the art, followed by the alkylation of the phenolic hydroxyl group with a radiolabeled electrophile such as ^{18}fluoroethyltosylate or ^{18}fluoroethylbromide to afford compound **B1**.

Scheme B



Other methods for incorporation of imaging molecules include, but are not limited to, alkylation, acylation with anhydrides and acid chlorides, coupling reactions with various carboxylic acids, reductive amination with aldehydes and ketones, and the like.

One skilled in the art will recognize that the foregoing examples describing the inclusion of desired radiolabels into the compounds of Formula (I) and (II) are not intended to be all inclusive, but rather are intended to provide examples of known chemistry using known synthetic methods.

An aspect of the present invention includes a composition comprising a compound of Formula (I), or pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable carrier. Compositions contemplated within this invention can be prepared according to conventional pharmaceutical techniques. A pharmaceutically acceptable carrier may also (but need not necessarily) be used in the composition of the invention.

The term "pharmaceutically acceptable" refers to molecular entities and compositions that do not produce an adverse, allergic or other untoward reaction when administered to an animal, or a human, as appropriate. Veterinary uses are equally included within the invention and "pharmaceutically acceptable" formulations include formulations for both clinical and/or veterinary use.

The composition may take a wide variety of forms depending on the form of preparation desired for administration including, but not limited to, intravenous (both bolus and infusion), oral, nasal, transdermal, topical with or without occlusion, and

injection intraperitoneally, subcutaneously, intramuscularly, intratumorally or parenterally, all using forms well known to those of ordinary skill in the pharmaceutical arts. The composition may comprise a dosage unit such as a tablet, pill, capsule, powder, granule, sterile parenteral solution or suspension, metered aerosol or liquid spray, drop, ampoule, auto-injector device or suppository; for administration orally, parenterally, intranasally, sublingually or rectally or by inhalation or insufflation. Compositions suitable for oral administration include solid forms such as pills, tablets, caplets, capsules (each including immediate release, timed release and sustained release formulations), granules and powders; and, liquid forms such as solutions, syrups, elixirs, emulsions and suspensions. Forms useful for parenteral administration include sterile solutions, emulsions and suspensions. Alternatively, the composition may be presented in a form suitable for once-weekly or once-monthly administration; for example, an insoluble salt of the active compound, such as the decanoate salt, may be adapted to provide a depot preparation for intramuscular injection. In preparing the compositions in oral dosage form, one or more of the usual pharmaceutical carriers may be employed, including necessary and inert pharmaceutical excipients, such as water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents, syrup and the like; in the case of oral liquid preparations, carriers such as starches, sugars, diluents, granulating agents, lubricants, binders, disintegrating agents and the like may be employed.

The dosage unit (tablet, capsule, powder, injection, suppository, measured liquid dosage and the like) containing the pharmaceutical compositions herein will contain an amount of the active ingredient necessary to deliver a therapeutically effective amount as described above. The composition may contain from about 0.001 mg to about 5000 mg of the active compound or prodrug thereof and may be constituted into any form suitable for the mode of administration selected for a subject in need.

An aspect of the present invention contemplates a therapeutically effective amount in a range of from about 0.001 mg to 1000 mg/kg of body weight per day. Another aspect of the present invention includes a range of from about 0.001 to about 500 mg/kg of body weight per day. A further aspect of the present invention includes a

range of from about 0.001 to about 300 mg/kg of body weight per day. The compounds may be administered according to a dosage regimen of from about 1 to about 5 times per day and still more preferably 1, 2 or 3 times a day.

For oral administration, the compositions are preferably provided in the form of tablets containing, 0.01,0.05, 0.1, 0.5, 1.0, 2.5, 5.0, 10.0, 15.0, 25.0, 50.0, 100, 150, 200, 250 and 500 milligrams of the active ingredient for the symptomatic adjustment of the dosage to the patient to be treated. Optimal dosages to be administered may be readily determined by those skilled in the art and will vary depending factors associated with the particular patient being treated (age, weight, diet and time of administration), the severity of the condition being treated, the compound being employed, the mode of administration and the strength of the preparation. The use of either daily administration or post-periodic dosing may be employed.

For preparing solid compositions such as tablets, the principal active ingredient is mixed with a pharmaceutical carrier, e.g. conventional tableting ingredients such as corn starch, lactose, sucrose, sorbitol, talc, stearic acid, magnesium stearate, dicalcium phosphate or gums and other pharmaceutical diluents, e.g. water, to form a solid preformulation composition containing a homogeneous mixture of a compound of the present invention, or a pharmaceutically acceptable salt thereof. When referring to these preformulation compositions as homogeneous, it is meant that the active ingredient is dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective dosage forms such as tablets, pills and capsules. This solid preformulation composition is then subdivided into unit dosage forms of the type described above containing from 0.001 to about 5000 mg of the active ingredient of the present invention. The tablets or pills of the composition can be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer that serves to resist disintegration in the stomach and permits the inner component to pass intact into the duodenum or to be delayed in release. A variety of material can be used for such

enteric layers or coatings, such materials including a number of polymeric acids with such materials as shellac, acetyl alcohol and cellulose acetate.

For oral administration in the form of a tablet or capsule, the active drug component can be optionally combined with an oral, non-toxic pharmaceutically acceptable inert carrier such as ethanol, glycerol, water and the like. Moreover, when desired or necessary, suitable binders; lubricants, disintegrating agents and coloring agents can also be incorporated into the mixture. Suitable binders include, without limitation, starch, gelatin, natural sugars such as glucose or beta-lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth or sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride and the like. Disintegrators include, without limitation, starch, methyl cellulose, agar, bentonite, xanthan gum and the like.

The liquid forms in which the compound of formula (I) may be incorporated for administration orally or by injection include, aqueous solutions, suitably flavored syrups, aqueous or oil suspensions and flavored emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil or peanut oil, as well as elixirs and similar pharmaceutical vehicles. Suitable dispersing or suspending agents for aqueous suspensions, include synthetic and natural gums such as tragacanth, acacia, alginate, dextran, sodium carboxymethylcellulose, methylcellulose, polyvinyl-pyrrolidone or gelatin. The liquid forms in suitably flavored suspending or dispersing agents may also include the synthetic and natural gums, for example, tragacanth, acacia, methyl-cellulose and the like. For parenteral administration, sterile suspensions and solutions are desired. Isotonic preparations that generally contain suitable preservatives are employed when intravenous administration is desired.

As is also known in the art, the compounds may alternatively be administered parenterally via injection of a formulation consisting of the active ingredient dissolved in an inert liquid carrier. The injectable formulation can include the active ingredient mixed with an appropriate inert liquid carrier. Acceptable liquid carriers include vegetable oils such as peanut oil, cottonseed oil, sesame oil and the like, as well as

organic solvents such as solketal, glycerol and the like. As an alternative, aqueous parenteral formulations may also be used. For example, acceptable aqueous solvents include water, Ringer's solution and an isotonic aqueous saline solution. Further, a sterile non-volatile oil can usually be employed as a solvent or suspending agent in the aqueous formulation. The formulations are prepared by dissolving or suspending the active ingredient in the liquid carrier such that the final formulation contains from 0.005 to 10% by weight of the active ingredient. Other additives including a preservative, an isotonizer, a solubilizer, a stabilizer and a pain-soothing agent may adequately be employed.

Advantageously, compounds of Formula (I) may be administered in a single daily dose, or the total daily dosage may be administered in divided doses of two, three or four times daily. Furthermore, compounds of the present invention can be administered in intranasal form via topical use of suitable intranasal vehicles, or via transdermal routes, using those forms of transdermal skin patches well known to those of ordinary skill in that art. To be administered in the form of a transdermal delivery system, the dosage administration will, of course, be continuous rather than intermittent throughout the dosage regimen.

Because of their ease of administration, tablets and capsules represent an advantageous oral dosage unit form, wherein solid pharmaceutical carriers are employed. If desired, tablets may be sugarcoated or enteric-coated by standard techniques. If desired, tablets may be sugar coated or enteric coated by standard techniques. For parenterals, the carrier will usually comprise sterile water, though other ingredients, for example, for purposes such as aiding solubility or for preservation, may be included. Injectable suspensions may also be prepared, in which case appropriate liquid carriers, suspending agents and the like may be employed.

The compositions of the present invention also include a composition for slow release of the compound of the invention. The composition includes a slow release carrier (typically, a polymeric carrier) and a compound of the invention. In preparation for slow release, a slow release carrier, typically a polymeric carrier and a compound of

the invention are first dissolved or dispersed in an organic solvent. The obtained organic solution is then added into an aqueous solution to obtain an oil-in-water-type emulsion. Preferably, the aqueous solution includes surface-active agent(s). Subsequently, the organic solvent is evaporated from the oil-in-water-type emulsion to obtain a colloidal suspension of particles containing the slow release carrier and the compound of the invention. Slow release biodegradable carriers are also well known in the art. These are materials that may form particles that capture therein an active compound(s) and slowly degrade/dissolve under a suitable environment (e.g., aqueous, acidic, basic, etc) and thereby degrade/dissolve in body fluids and release the active compound(s) therein. The particles are preferably nanoparticles (i.e., in the range of about 1 to 500 nm in diameter, preferably about 50-200 nm in diameter and most preferably about 100 nm in diameter).

The present invention also provides methods to prepare the pharmaceutical compositions of this invention. A compound of Formula (I) as the active ingredient is intimately admixed with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques, which carrier may take a wide variety of forms depending on the form of preparation desired for administration. In preparing the compositions in oral dosage form, any of the usual pharmaceutical media may be employed. For solid oral dosage forms, suitable carriers and additives include starches, sugars, diluents, granulating agents, lubricants, binders, disintegrating agents and the like. For liquid oral preparations, suitable carriers and additives include water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents and the like. Additionally, liquid forms of the active drug component can be combined in suitably flavored suspending or dispersing agents such as the synthetic and natural gums, including for example, tragacanth, acacia, methyl-cellulose and the like. Other dispersing agents that may be employed include glycerin and the like.

The compounds of the present invention can also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles and multilamellar vesicles. Liposomes containing delivery systems as well known in the art are formed from a variety of phospholipids, such as cholesterol,

stearylamine or phosphatidylcholines.

2. Targeting Ligands and Targeting Conjugates

Another embodiment of the present invention relates to the synthesis and biological application of piperidinoyl carboxylic acid integrin antagonists targeting ligands. These targeting ligands maybe used with imaging agents (radioactive labeling reagents and the like) or liposomes to target cells that express the $\alpha_V\beta_3$, $\alpha_V\beta_5$, or $\alpha_V\beta_6$ integrin receptors.

The targeting ligands and targeting conjugates of the present invention will employ any of the previously defined substituents for W, R_1, R_{1a}, R_4, R_5, R_6, R_7, R_8, R_9, R_{10}, q, and Z in any combination, with the appropriate substitutions of R_{2a}, R_{14}, R_{11}, R_{12}, and R_{13}, for the targeting ligand and targeting conjugate respectively. Preferred embodiments for R_{2a} R_{14}, R_{11}, R_{12}, and R_{13}, are provided hereinafter.

Aspects of the present invention include targeting ligands and targeting conjugates of Formula (I) and Formula (II) wherein the variables of the formulas are as previously described and R_{2a} is -$C_{1\text{-}4}$alkyl(R_7)(R_{11}), -$C_{2\text{-}4}$alkenyl(R_7)(R_{11}),, -$C_{2\text{-}4}$alkynyl(R_7)(R_{11}),, -cycloalkyl(R_8)(R_{12}), -heterocyclyl(R_8)(R_{12}) , -aryl(R_8)(R_{12}) or -heteroaryl(R_8)(R_{12}).

Another aspect of the present invention includes targeting ligands and targeting conjugates of Formula (I) and Formula (II) wherein the variables of the formulas are as previously described and R_{2a} is -cycloalkyl(R_8)(R_{12}), -heterocyclyl(R_8)(R_{12}), -aryl(R_8)(R_{12}) or -heteroaryl(R_8)(R_{12}).

Another aspect of the present invention includes targeting ligands and targeting conjugates of Formula (I) and Formula (II) wherein the variables of the formulas are as previously described and R_{2a} is -cycloalkyl(R_8)(R_{11}), -heterocyclyl(R_8)(R_{12}), -phenyl(R_8)(R_{12}), -naphthalenyl(R_8)(R_{12}) or -heteroaryl(R_8)(R_{12}).

Another aspect of the present invention includes targeting ligands and targeting conjugates of Formula (I) and Formula (II) wherein the variables of the formulas are as previously described and R_{2a} is -tetrahydropyrimidinyl(R_8)(R_{12}), -1,3-benzodioxolyl(R_8)(R_{12}), -dihydrobenzofuranyl(R_8)(R_{12}), -tetrahydroquinolinyl(R_8)(R_{12}), -phenyl(R_8)(R_{12}), -naphthalenyl(R_8)(R_{12}), -pyridinyl(R_8)(R_{12}), -pyrimidinyl(R_8)(R_{12}) or -quinolinyl(R_8)(R_{12}).

A further aspects of the present invention include targeting ligands as previously defined of Formula (I) and Formula (II) wherein the variables are as previously defined and R_{11} is selected from the group consisting of -C_{1-8}alkyl(R_{14}), -O-C_{1-8}alkyl(R_{14}), -NH-C_{1-8}alkyl(R_{14}), -S-C_{1-8}alkyl(R_{14}), -C(=O)C_{1-8}alkyl(R_{14}), -O-C(=O)C_{1-8}alkyl(R_{14}), -NH-C(=O)C_{1-8}alkyl(R_{14}), -C(=O)OC_{1-8}alkyl(R_{14}), -C(=O)NHC_{1-8}alkyl(R_{14}), -O-C(=O)OC_{1-8}alkyl(R_{14}), -O-C(=O)NHC_{1-8}alkyl(R_{14}), -O-C(=O)C_{1-8}alkylC(=O)(R_{14}), -NH-C(=O)C_{1-8}alkylC(=O)(R_{14}), -C(=O)OC_{1-8}alkylC(=O)(R_{14}), -O-C(=O)OC_{1-8}alkylC(=O)(R_{14}), -NH-C(=O)OC_{1-8}alkylC(=O)(R_{14}), -C(=O)NHC_{1-8}alkylC(=O)(R_{14}), -O-C(=O)NHC_{1-8}alkylC(=O)(R_{14}), -NH-C(=O)NHC_{1-8}alkylC(=O)(R_{14}), -$SCH_2CH_2O(CH_2CH_2O)_rCH_2CH_2$($R_{14}$), -$NHCH_2CH_2O(CH_2CH_2O)_rCH_2C$(=O)($R_{14}$), -$SO_2NHCH_2CH_2O(CH_2CH_2O)_rCH_2CH_2$($R_{14}$), -C(=O)$CH_2O(CH_2CH_2O)_rCH_2C$(=O)($R_{14}$), -OC(=O)$OCH_2CH_2O(CH_2CH_2O)_rCH_2C$(=O)($R_{14}$), -OC(=O)$NHCH_2CH_2O(CH_2CH_2O)_rCH_2C$(=O)($R_{14}$), -NHC(=O)$NHCH_2CH_2O(CH_2CH_2O)_rCH_2C$(=O)($R_{14}$), and -$SO_2NHCH_2CH_2O(CH_2CH_2O)_rCH_2C$(=O)($R_{14}$).

Aspects of the present invention include targeting ligands of Formula (I) and Formula (II) wherein the variables are as previously defined and R_{11} is selected from the group consisting of -C_{1-8}alkyl(R_{14}), -O-C_{1-8}alkyl(R_{14}), -NH-C_{1-8}alkyl(R_{14}), -S-C_{1-8}alkyl(R_{14}), -C(=O)C_{1-8}alkyl(R_{14}), -O-C(=O)C_{1-8}alkyl(R_{14}), -NH-C(=O)C_{1-8}alkyl(R_{14}), -C(=O)OC_{1-8}alkyl(R_{14}), -C(=O)NHC_{1-8}alkyl(R_{14}), -O-C(=O)OC_{1-8}alkyl(R_{14}), -O-C(=O)NHC_{1-8}alkyl(R_{14}),

$-O-C(=O)C_{1-8}alkylC(=O)(R_{14})$, $-NH-C(=O)C_{1-8}alkylC(=O)(R_{14})$, $-C(=O)OC_{1-8}alkylC(=O)(R_{14})$, $-O-C(=O)OC_{1-8}alkylC(=O)(R_{14})$, $-NH-C(=O)OC_{1-8}alkylC(=O)(R_{14})$, $-C(=O)NHC_{1-8}alkylC(=O)(R_{14})$, $-O-C(=O)NHC_{1-8}alkylC(=O)(R_{14})$, and $-NH-C(=O)NHC_{1-8}alkylC(=O)(R_{14})$.

Aspects of the present invention include targeting ligands of Formula (I) and Formula (II) wherein the variables are as previously defined and R_{12} is selected from the group consisting of $-C_{1-6}alkyl(R_{14})$, $-O-C_{1-6}alkyl(R_{14})$, $-NH-C_{1-4}alkyl(R_{14})$, $-S-C_{1-6}alkyl(R_{14})$, $-CH_2O-C_{1-6}alkyl(R_{14})$, $-CH_2NH-C_{1-6}alkyl(R_{14})$, $-CH_2S-C_{1-6}alkyl(R_{14})$, $-C(=O)C_{1-6}alkyl(R_{14})$, $-O-C(=O)C_{1-6}alkyl(R_{14})$, $-NH-C(=O)C_{1-8}alkyl(R_{14})$, $-CH_2O-C(=O)C_{1-8}alkyl(R_{14})$, $-CH_2NH-C(=O)C_{1-6}alkyl(R_{14})$, $-C(=O)OC_{1-6}alkyl(R_{14})$, $-C(=O)NHC_{1-6}alkyl(R_{14})$, $-O-C(=O)OC_{1-6}alkyl(R_{14})$, $-O-C(=O)NHC_{1-6}alkyl(R_{14})$, $-NH-C(=O)OC_{1-6}alkyl(R_{14})$, $-NH-C(=O)NHC_{1-6}alkyl(R_{14})$, $-NH-C(=O)C_{1-6}alkylC(=O)(R_{14})$, $-CH_2O-C(=O)C_{1-8}alkylC(=O)(R_{14})$, $-NH-C(=O)NHC_{1-8}alkylC(=O)(R_{14})$, $-CH_2O-C(=O)NHC_{1-8}alkylC(=O)(R_{14})$, $-CH_2NH-C(=O)NHC_{1-8}alkylC(=O)(R_{14})$, $-OCH_2CH_2O(CH_2CH_2O)_rCH_2CH_2(R_{14})$, $-NHCH_2CH_2O(CH_2CH_2O)_rCH_2CH_2(R_{14})$, $-SCH_2CH_2O(CH_2CH_2O)_rCH_2CH_2(R_{14})$, $-OCH_2CH_2O(CH_2CH_2O)_rCH_2C(=O)(R_{14})$, $-NHCH_2CH_2O(CH_2CH_2O)_rCH_2C(=O)(R_{14})$, $-OC(=O)NHCH_2CH_2O(CH_2CH_2O)_rCH_2CH_2(R_{14})$, $-NH(C=O)CH_2O(CH_2CH_2O)_rCH_2CH_2(R_{14})$, $-NHC(=O)OCH_2CH_2O(CH_2CH_2O)_rCH_2CH_2(R_{14})$, $-NHC(=O)NHCH_2CH_2O(CH_2CH_2O)_rCH_2CH_2(R_{14})$, $-SO_2CH_2CH_2O(CH_2CH_2O)_rCH_2CH_2(R_{14})$, $-SO_2NHCH_2CH_2O(CH_2CH_2O)_rCH_2CH_2(R_{14})$, $-CH_2OCH_2CH_2O(CH_2CH_2O)_rCH_2CH_2(R_{14})$, $-CH_2NHCH_2CH_2O(CH_2CH_2O)_rCH_2CH_2(R_{14})$, $-CH_2SCH_2CH_2O(CH_2CH_2O)_rCH_2CH_2(R_{14})$,

$-CH_2OCH_2CH_2O(CH_2CH_2O)_rCH_2C(=O)(R_{14})$,
$-OC(=O)NHCH_2CH_2O(CH_2CH_2O)_rCH_2C(=O)(R_{14})$,
$-NH(C=O)CH_2O(CH_2CH_2O)_rCH_2C(=O)(R_{14})$,
$-NHC(=O)OCH_2CH_2O(CH_2CH_2O)_rCH_2C(=O)(R_{14})$,
$-NHC(=O)NHCH_2CH_2O(CH_2CH_2O)_rCH_2C(=O)(R_{14})$,
$-CH_2OC(=O)CH_2O(CH_2CH_2O)_rCH_2C(=O)(R_{14})$,
$-CH_2NH(C=O)CH_2O(CH_2CH_2O)_rCH_2C(=O)(R_{14})$,
$-CH_2NHC(=O)OCH_2CH_2O(CH_2CH_2O)_rCH_2C(=O)(R_{14})$, and
$-CH_2NHC(=O)NHCH_2CH_2O(CH_2CH_2O)_rCH_2C(=O)(R_{14})$.

In another aspect of the present invention includes targeting ligands of Formula (I) and Formula (II) wherein the variables of the formula are as previously defined and $R_{14}$when R_{11} and R_{12} terminates with a C(=O)is selected from the group consisting of hydrogen, OH, $-OC_{1-4}alkyl$ and NH_2; otherwise $R_{14}$is selected from the group consisting of -OH, -SH, COOH, and $-COOC_{1-4}alkyl$.

A further aspects of the present invention include targeting conjugates as previously defined of Formula (I) and Formula (II) wherein the variables are as previously defined and R_{11} is selected from the group consisting of $-C_{1-8}alkyl(R_{13})$, $-O-C_{1-8}alkyl(R_{13})$, $-NH-C_{1-8}alkyl(R_{13})$, $-S-C_{1-8}alkyl(R_{13})$, $-C(=O)C_{1-8}alkyl(R_{13})$, $-O-C(=O)C_{1-8}alkyl(R_{13})$, $-NH-C(=O)C_{1-8}alkyl(R_{13})$, $-C(=O)OC_{1-8}alkyl(R_{13})$, $-C(=O)NHC_{1-8}alkyl(R_{13})$, $-O-C(=O)OC_{1-8}alkyl(R_{13})$, $-O-C(=O)NHC_{1-8}alkyl(R_{13})$, $-O-C(=O)C_{1-8}alkylC(=O)(R_{13})$, $-NH-C(=O)C_{1-8}alkylC(=O)(R_{13})$, $-C(=O)OC_{1-8}alkylC(=O)(R_{13})$, $-O-C(=O)OC_{1-8}alkylC(=O)(R_{13})$, $-NH-C(=O)OC_{1-8}alkylC(=O)(R_{13})$, $-C(=O)NHC_{1-8}alkylC(=O)(R_{13})$, $-O-C(=O)NHC_{1-8}alkylC(=O)(R_{13})$, $-NH-C(=O)NHC_{1-8}alkylC(=O)(R_{13})$,
$-SCH_2CH_2O(CH_2CH_2O)_rCH_2CH_2(R_{13})$,
$-NHCH_2CH_2O(CH_2CH_2O)_rCH_2C(=O)(R_{13})$,
$-SO_2NHCH_2CH_2O(CH_2CH_2O)_rCH_2CH_2(R_{13})$,
$-C(=O)CH_2O(CH_2CH_2O)_rCH_2C(=O)(R_{13})$,
$-OC(=O)OCH_2CH_2O(CH_2CH_2O)_rCH_2C(=O)(R_{13})$,
$-OC(=O)NHCH_2CH_2O(CH_2CH_2O)_rCH_2C(=O)(R_{13})$,

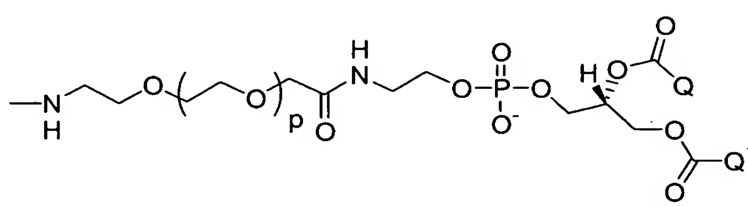
$-NHC(=O)NHCH_2CH_2O(CH_2CH_2O)_rCH_2C(=O)(R_{13})$, and $-SO_2NHCH_2CH_2O(CH_2CH_2O)_rCH_2C(=O)(R_{13})$.

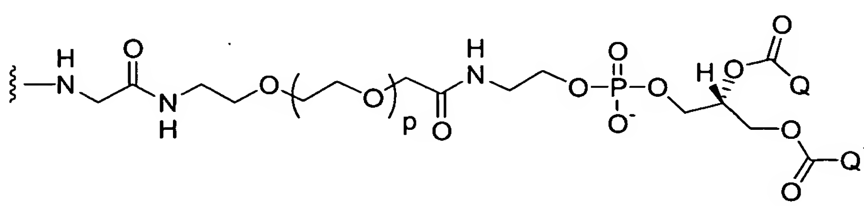
Aspects of the present invention include targeting conjugates of Formula (I) and Formula (II) wherein the variables are as previously defined and R_{11} is selected from the group consisting of $-C_{1-8}alkyl(R_{13})$, $-O-C_{1-8}alkyl(R_{13})$, $-NH-C_{1-8}alkyl(R_{13})$, $-S-C_{1-8}alkyl(R_{13})$, $-C(=O)C_{1-8}alkyl(R_{13})$, $-O-C(=O)C_{1-8}alkyl(R_{13})$, $-NH-C(=O)C_{1-8}alkyl(R_{13})$, $-C(=O)OC_{1-8}alkyl(R_{13})$, $-C(=O)NHC_{1-8}alkyl(R_{13})$, $-O-C(=O)OC_{1-8}alkyl(R_{13})$, $-O-C(=O)NHC_{1-8}alkyl(R_{13})$, $-O-C(=O)C_{1-8}alkylC(=O)(R_{13})$, $-NH-C(=O)C_{1-8}alkylC(=O)(R_{13})$, $-C(=O)OC_{1-8}alkylC(=O)(R_{13})$, $-O-C(=O)OC_{1-8}alkylC(=O)(R_{13})$, $-NH-C(=O)OC_{1-8}alkylC(=O)(R_{13})$, $-C(=O)NHC_{1-8}alkylC(=O)(R_{13})$, $-O-C(=O)NHC_{1-8}alkylC(=O)(R_{13})$, and $-NH-C(=O)NHC_{1-8}alkylC(=O)(R_{13})$.

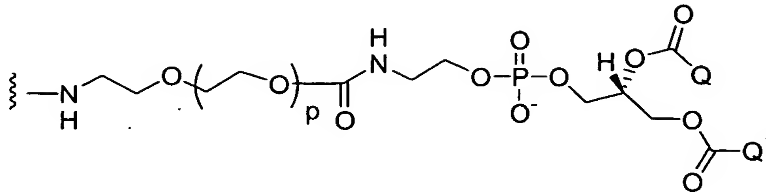
Aspects of the present invention include targeting conjugates of Formula (I) and Formula (II) wherein the variables are as previously defined and R_{12} is selected from the group consisting of $-C_{1-6}alkyl(R_{13})$, $-O-C_{1-6}alkyl(R_{13})$, $-NH-C_{1-4}alkyl(R_{13})$, $-S-C_{1-6}alkyl(R_{13})$, $-CH_2O-C_{1-6}alkyl(R_{13})$, $-CH_2NH-C_{1-6}alkyl(R_{13})$, $-CH_2S-C_{1-6}alkyl(R_{13})$, $-C(=O)C_{1-6}alkyl(R_{13})$, $-O-C(=O)C_{1-6}alkyl(R_{13})$, $-NH-C(=O)C_{1-8}alkyl(R_{13})$, $-CH_2O-C(=O)C_{1-8}alkyl(R_{13})$, $-CH_2NH-C(=O)C_{1-6}alkyl(R_{13})$, $-C(=O)OC_{1-6}alkyl(R_{13})$, $-C(=O)NHC_{1-6}alkyl(R_{13})$, $-O-C(=O)OC_{1-6}alkyl(R_{13})$, $-O-C(=O)NHC_{1-6}alkyl(R_{13})$, $-NH-C(=O)OC_{1-6}alkyl(R_{13})$, $-NH-C(=O)NHC_{1-6}alkyl(R_{13})$, $-NH-C(=O)C_{1-6}alkylC(=O)(R_{13})$, $-CH_2O-C(=O)C_{1-8}alkylC(=O)(R_{13})$, $-NH-C(=O)NHC_{1-8}alkylC(=O)(R_{13})$, $-CH_2O-C(=O)NHC_{1-8}alkylC(=O)(R_{13})$, $-CH_2NH-C(=O)NHC_{1-8}alkylC(=O)(R_{13})$, $-OCH_2CH_2O(CH_2CH_2O)_rCH_2CH_2(R_{13})$, $-NHCH_2CH_2O(CH_2CH_2O)_rCH_2CH_2(R_{13})$, $-SCH_2CH_2O(CH_2CH_2O)_rCH_2CH_2(R_{13})$, $-OCH_2CH_2O(CH_2CH_2O)_rCH_2C(=O)(R_{13})$, $-NHCH_2CH_2O(CH_2CH_2O)_rCH_2C(=O)(R_{13})$,

$-OC(=O)NHCH_2CH_2O(CH_2CH_2O)_rCH_2CH_2(R_{13})$,
$-NH(C=O)CH_2O(CH_2CH_2O)_rCH_2CH_2(R_{13})$,
$-NHC(=O)OCH_2CH_2O(CH_2CH_2O)_rCH_2CH_2(R_{13})$,
$-NHC(=O)NHCH_2CH_2O(CH_2CH_2O)_rCH_2CH_2(R_{13})$,
$-SO_2CH_2CH_2O(CH_2CH_2O)_rCH_2CH_2(R_{13})$,
$-SO_2NHCH_2CH_2O(CH_2CH_2O)_rCH_2CH_2(R_{13})$,
$-CH_2OCH_2CH_2O(CH_2CH_2O)_rCH_2CH_2(R_{13})$,
$-CH_2NHCH_2CH_2O(CH_2CH_2O)_rCH_2CH_2(R_{13})$,
$-CH_2SCH_2CH_2O(CH_2CH_2O)_rCH_2CH_2(R_{13})$,
$-CH_2OCH_2CH_2O(CH_2CH_2O)_rCH_2C(=O)(R_{13})$,
$-OC(=O)NHCH_2CH_2O(CH_2CH_2O)_rCH_2C(=O)(R_{13})$,
$-NH(C=O)CH_2O(CH_2CH_2O)_rCH_2C(=O)(R_{13})$,
$-NHC(=O)OCH_2CH_2O(CH_2CH_2O)_rCH_2C(=O)(R_{13})$,
$-NHC(=O)NHCH_2CH_2O(CH_2CH_2O)_rCH_2C(=O)(R_{13})$,
$-CH_2OC(=O)CH_2O(CH_2CH_2O)_rCH_2C(=O)(R_{13})$,
$-CH_2NH(C=O)CH_2O(CH_2CH_2O)_rCH_2C(=O)(R_{13})$,
$-CH_2NHC(=O)OCH_2CH_2O(CH_2CH_2O)_rCH_2C(=O)(R_{13})$, and
$-CH_2NHC(=O)NHCH_2CH_2O(CH_2CH_2O)_rCH_2C(=O)(R_{13})$;

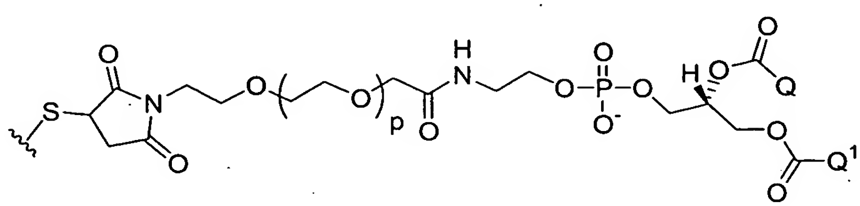
wherein when R_{11} or R_{12} terminates with a $-C(=O)-$, R_{13} is selected from the group consisting of

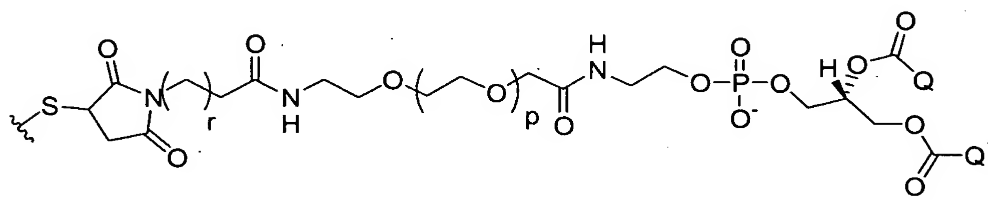

,

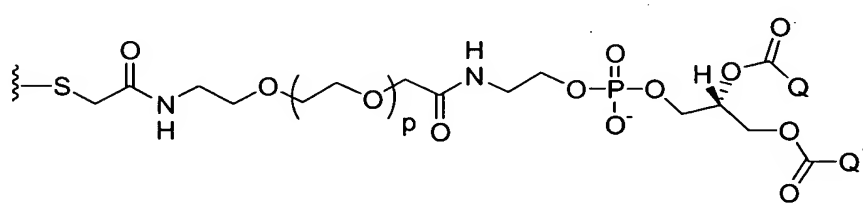

, and

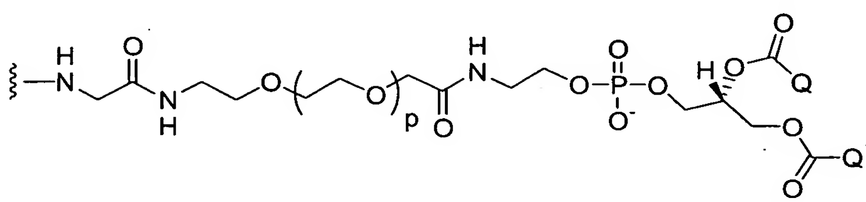

;

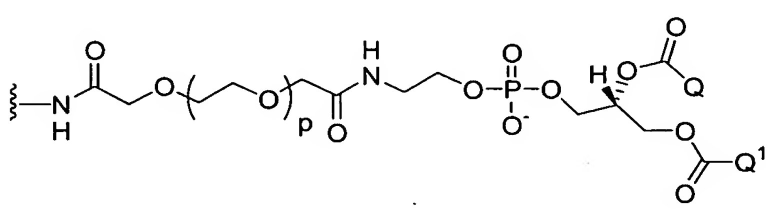
and when R_{11} or R_{12} does not terminate with a –C(=O)-, R_{13} is selected from the group consisting of

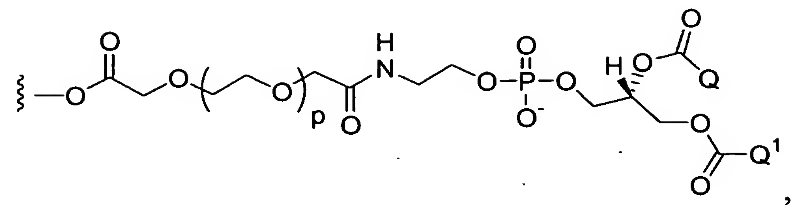

,

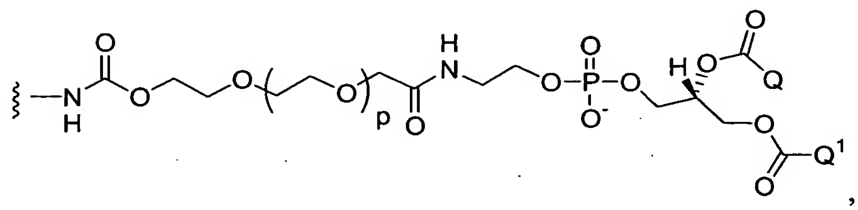

,

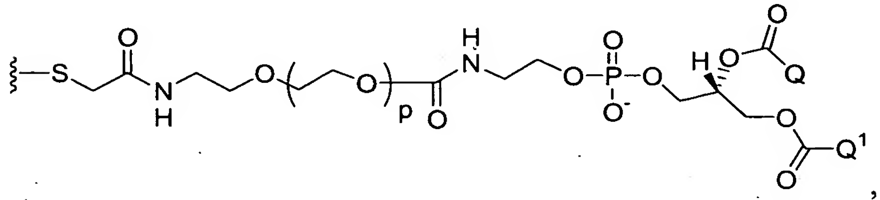

,

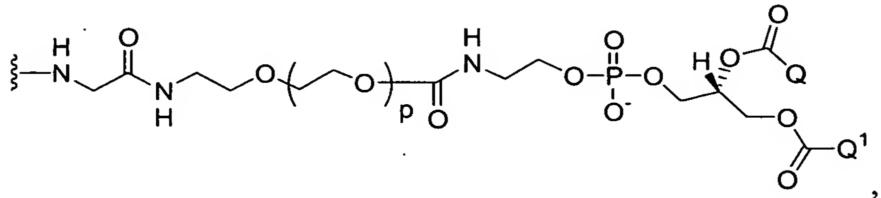

,

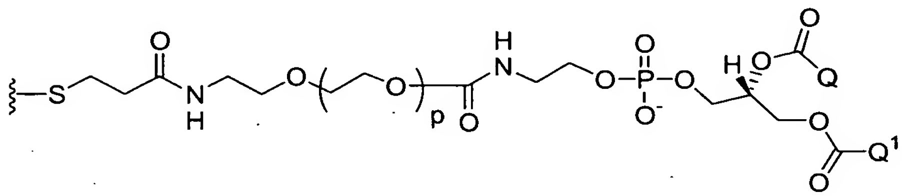

,

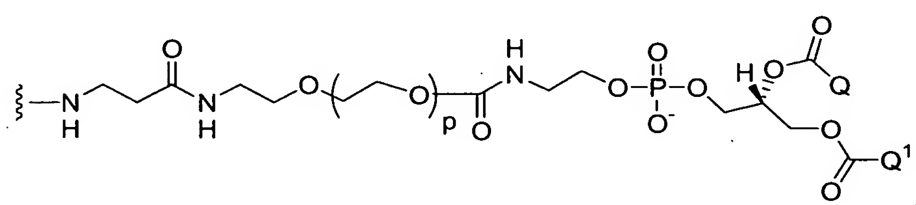


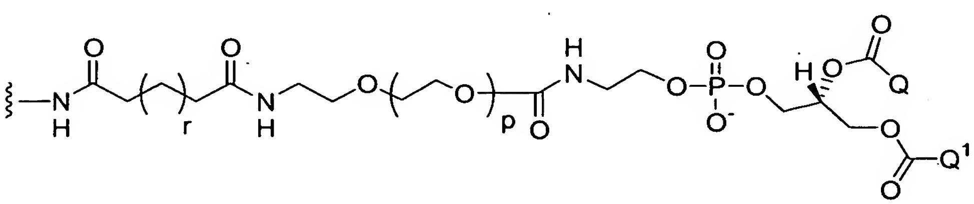


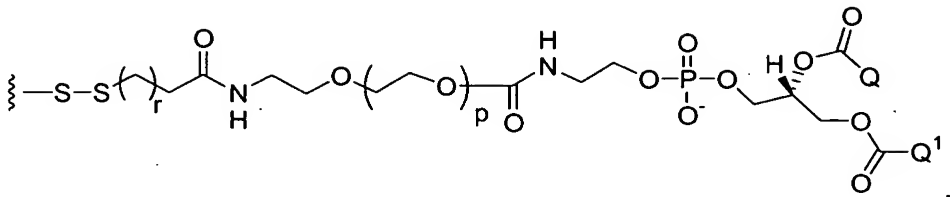




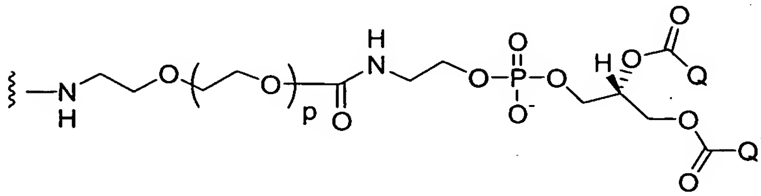




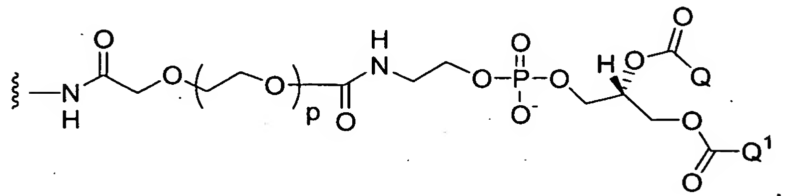




,



, and



.

Aspects of the present invention include compounds of Formula (I) and Formula (II) wherein the variables are as previously defined and R_{12} is selected from the group consisting of

-CH_2O-C_{1-6}alkyl(R_{13}),

-CH_2NH-C_{1-6}alkyl(R_{13}), -CH_2S-C_{1-6}alkyl(R_{13}),

-NH-C(=O)C_{1-8}alkyl(R_{13}),

-CH_2NH-C(=O)C_{1-6}alkyl(R_{13}),

-NH-C(=O)NHC_{1-6}alkyl(R_{13}),

-NH-C(=O)C_{1-6}alkylC(=O)(R_{13}),

-$OCH_2CH_2O(CH_2CH_2O)_rCH_2CH_2$($R_{13}$),

-$NHCH_2CH_2O(CH_2CH_2O)_rCH_2CH_2$($R_{13}$),

-$OCH_2CH_2O(CH_2CH_2O)_rCH_2C$(=O)($R_{13}$),

-NH(C=O)$CH_2O(CH_2CH_2O)_rCH_2CH_2$($R_{13}$),

-$CH_2OCH_2CH_2O(CH_2CH_2O)_rCH_2CH_2$($R_{13}$),

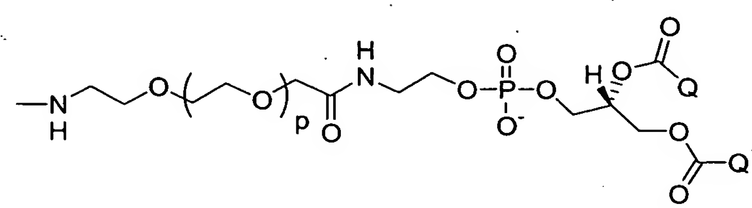
-$CH_2NHCH_2CH_2O(CH_2CH_2O)_rCH_2CH_2$($R_{13}$),

-$CH_2SCH_2CH_2O(CH_2CH_2O)_rCH_2CH_2$($R_{13}$),

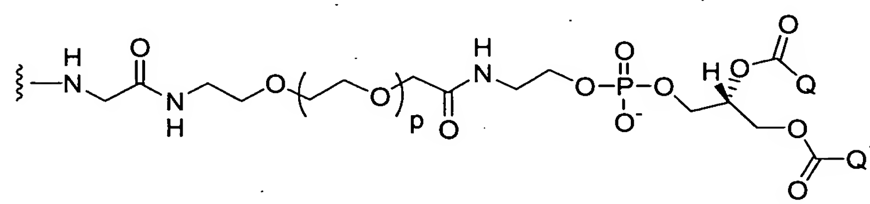
-NH(C=O)$CH_2O(CH_2CH_2O)_rCH_2C$(=O)(R_{13}), and

-CH_2NH(C=O)$CH_2O(CH_2CH_2O)_rCH_2C$(=O)(R_{13}).

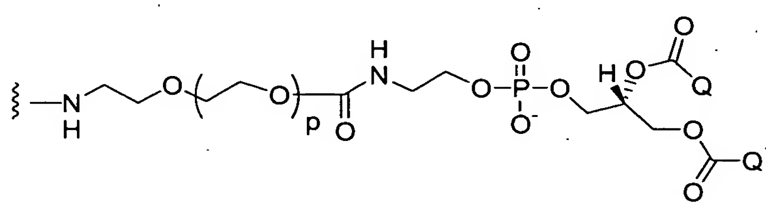
wherein when R_{11} or R_{12} terminates with a –C(=O)-, R_{13} is selected from the group consisting of



,

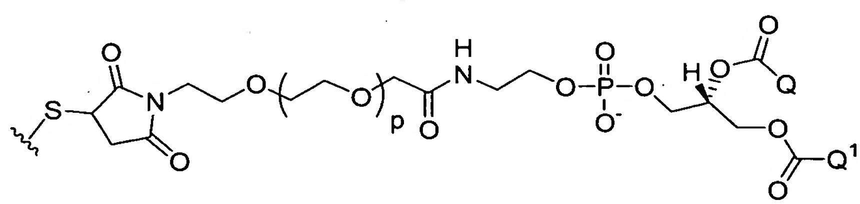


, and

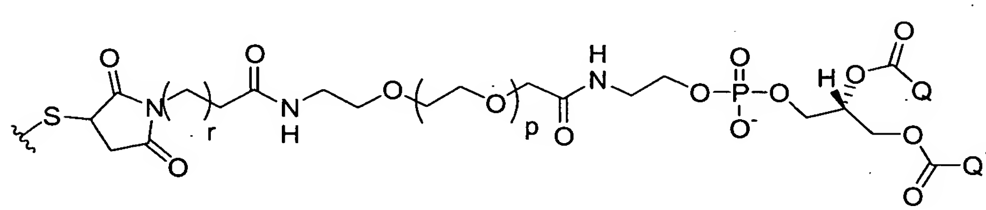


;

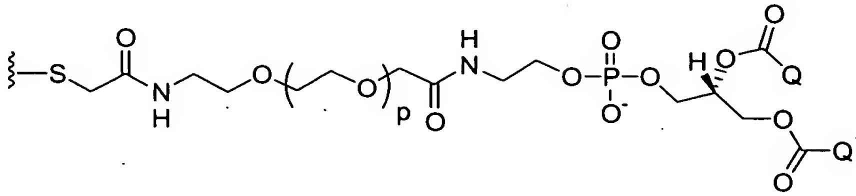
and when R_{11} or R_{12} does not terminate with a –C(=O)-, R_{13} is selected from the group consisting of

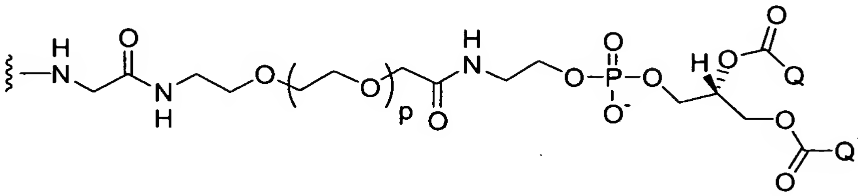


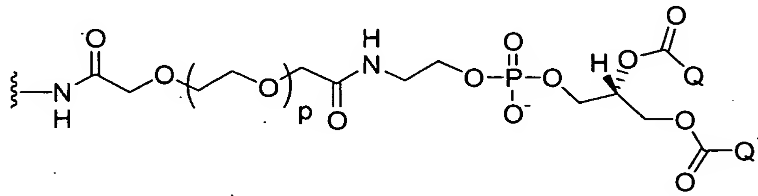
,

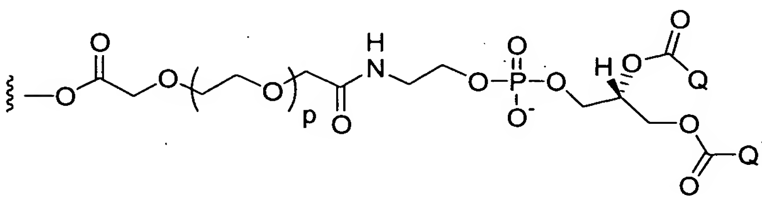


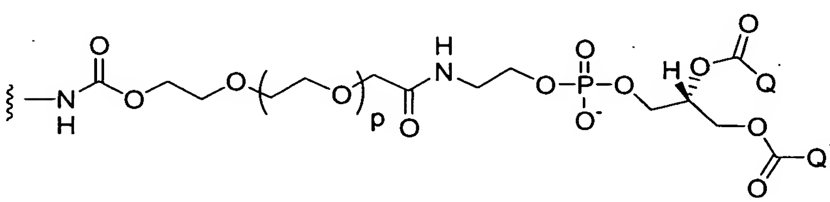
,

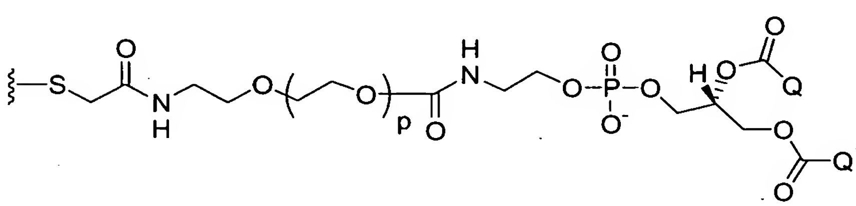

,

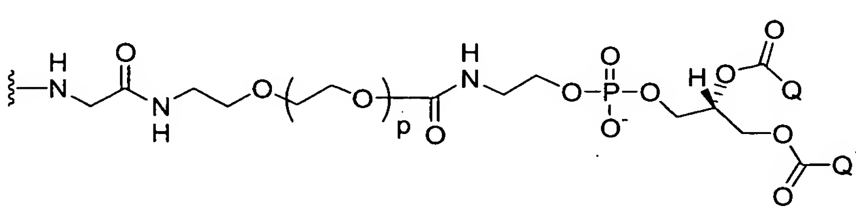

,

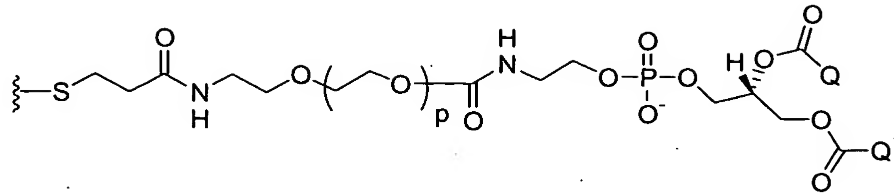

,


,

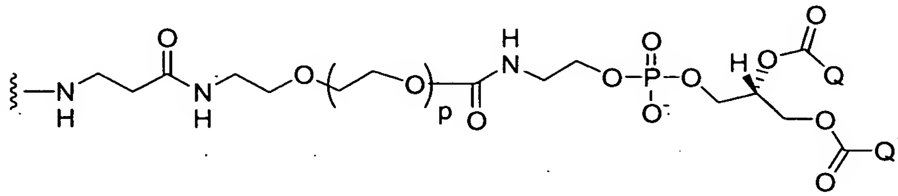

,


,

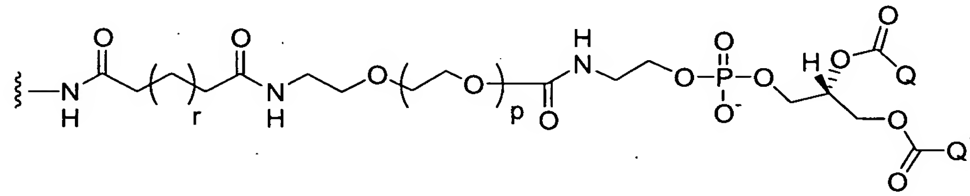

,



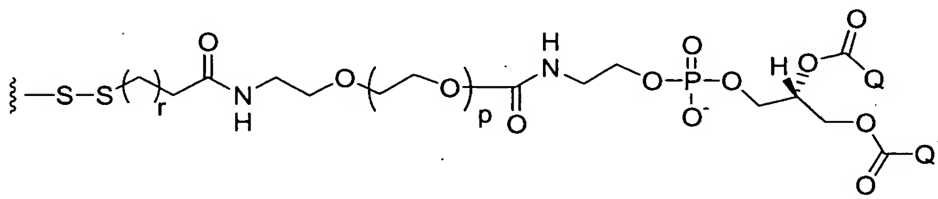
,



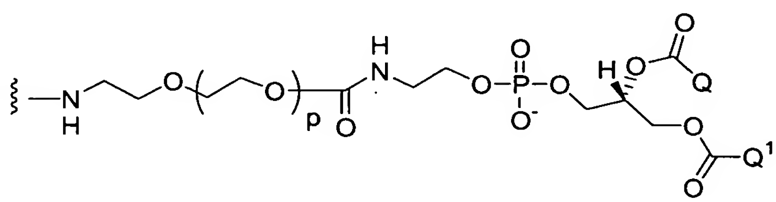
,



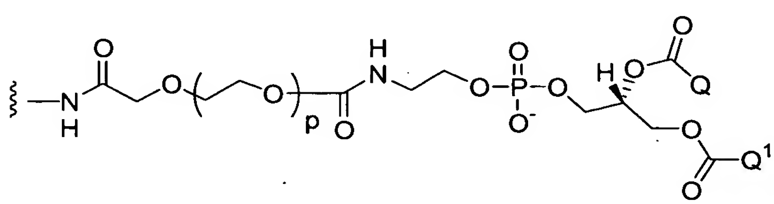
,



,



, and



.

Aspects of the present invention include targeting conjugates of Formula (I) and Formula (II) wherein the variables are as previously defined and R_{12} is selected from the group consisting of

$-CH_2-O-(CH_2)_4(R_{13})-$,

$-CH_2-NH-(CH_2)_4(R_{13})-$,

$-CH_2-S-(CH_2)_4(R_{13})-$,

$-CH_2-O-(CH_2)_6(R_{13})-$,

$-CH_2-NH-(CH_2)_6(R_{13})-$,

$-CH_2-S-(CH_2)_6(R_{13})-$,

$-NH-C(=O)-(CH_2)_4(R_{13})-$,

$-NH-C(=O)-(CH_2)_7(R_{13})-$,

$-NH-C(=O)NH-(CH_2)_3(R_{13})-$,

$-NH-C(=O)NH-(CH_2)_6(R_{13})-$,

$-CH_2NH-C(=O)NH-(CH_2)_2(R_{13})-$,

$-CH_2NH-C(=O)NH-(CH_2)_5(R_{13})-$,

$-NHC(=O)-(CH_2)_2-C(=O)(R_{13})-$,

$-NHC(=O)-(CH_2)_3-C(=O)(R_{13})-$,

$-NHC(=O)-(CH_2)_4-C(=O)(R_{13})-$,

$-OCH_2CH_2OCH_2CH_2(R_{13})-$,

$-NHCH_2CH_2OCH_2CH_2(R_{13})-$,

$-OCH_2CH_2OCH_2CH_2OCH_2CH_2(R_{13})-$,

$-NHCH_2CH_2OCH_2CH_2OCH_2CH_2(R_{13})-$,

$-OCH_2CH_2OCH_2C(=O)(R_{13})-$,

$-OCH_2CH_2OCH_2CH_2OCH_2C(=O)(R_{13})-$,

$-NHC(=O)CH_2OCH_2CH_2(R_{13})-$,

$-NHC(=O)CH_2OCH_2CH_2OCH_2CH_2(R_{13})-$,

$-CH_2OCH_2CH_2OCH_2CH_2(R_{13})-$,

$-CH_2NHCH_2CH_2OCH_2CH_2(R_{13})-$,

$-CH_2SCH_2CH_2OCH_2CH_2(R_{13})-$,

$-CH_2OCH_2CH_2OCH_2CH_2OCH_2CH_2(R_{13})-$,

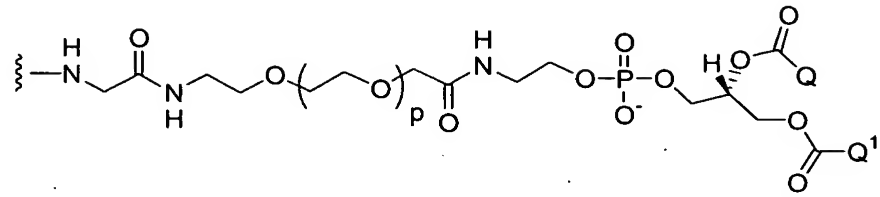
$-CH_2NHCH_2CH_2OCH_2CH_2OCH_2CH_2(R_{13})-$,

$-CH_2SCH_2CH_2OCH_2CH_2OCH_2CH_2(R_{13})-$,

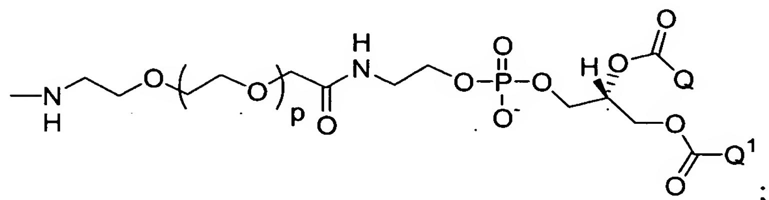
$-CH_2NHC(=O)CH_2OCH_2C(=O)(R_{13})-$, and

$-NHC(=O)CH_2OCH_2C(=O)(R_{13})-$;

wherein when R_{11} or R_{12} terminates with a $-C(=O)-$, R_{13} is selected from the group consisting of

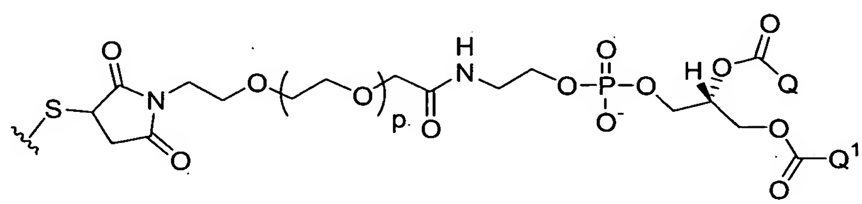


and

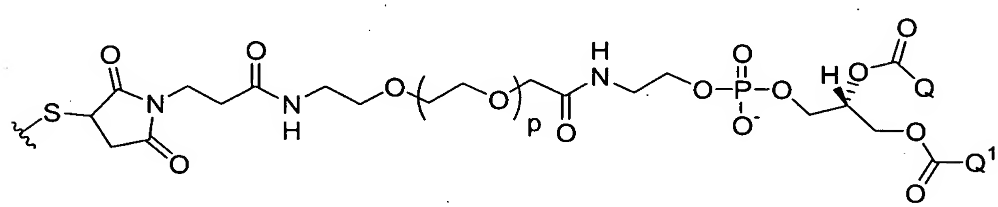


;

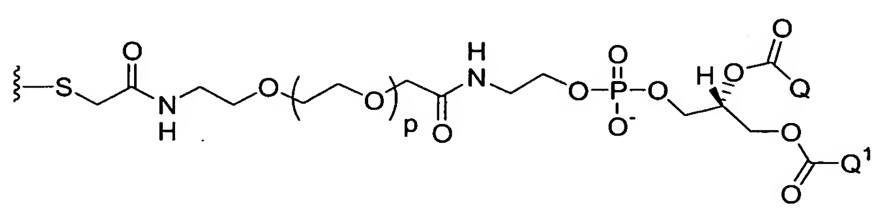
and when R_{11} or R_{12} does not terminate with a –C(=O)-, R_{13} is selected from the group consisting of



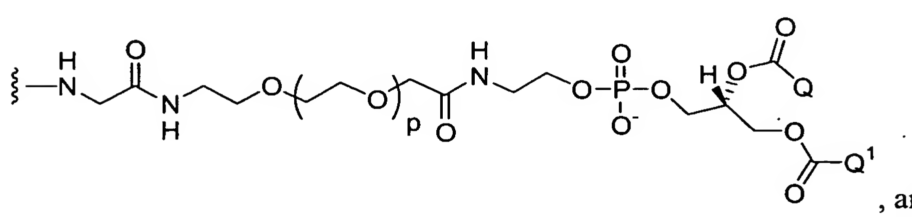
,



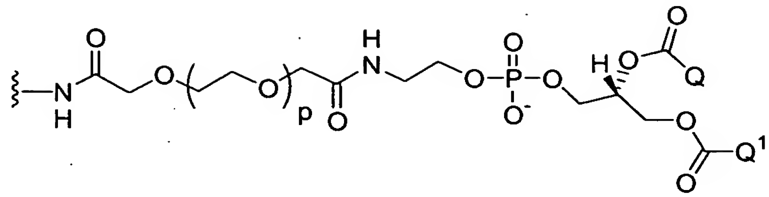
,

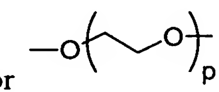


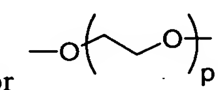
,

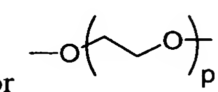


, and



Aspects of the present invention include a composition comprising a compound of Formula (I) and Formula (II) wherein said –O-(CH_2CH_2O-)$_p$- or  of R_{12} and R_{13} is a polyethylene glycol (PEG) polymer ranging in molecular weight from 750 to 5000 daltons.

Aspects of the present invention include a composition comprising a compound of Formula (I) and Formula (II) wherein said –O-(CH_2CH_2O-)$_p$- or  of R_{12} and R_{13} is a polyethylene glycol (PEG) polymer ranging in molecular weight from 2000 to 5000 daltons.

Aspects of the present invention include a composition comprising a compound of Formula (I) and Formula (II) wherein said –O-(CH_2CH_2O-)$_p$- or  of R_{12} and R_{13} is a polyethylene glycol (PEG) polymer selected from 2000 (PEG 2000), 3400 (PEG 3400), or 5000 (PEG 5000) daltons.

Aspects of the present invention include a composition comprising a compound of Formula (I) and Formula (II) wherein r is an integer from 0 to 8.

Aspects of the present invention include a composition comprising a compound of Formula (I) and Formula (II) wherein Q and Q^1 of substituents R_{12} and R_{13} are the same within a given compound and are selected from the group consisting of
the C_{11} saturated chain of lauric acid,
the C_{15} saturated chain of palmitoic acid,
the C_{17} saturated chain of stearoic acid,

the C_{17} mono-unsaturated chain of oleoic acid, and
the C_{17} di-unsaturated chain of linoleic acid.

Aspects of the present invention include a composition comprising a compound of Formula (I) and Formula (II) wherein Q and Q^1 of substituents R_{12} and R_{13} are the same within a given compound and are selected from the group consisting of
the C_{15} saturated chain of palmitoic acid,
the C_{17} saturated chain of stearoic acid, and
the C_{17} mono-unsaturated chain of oleoic acid.

Aspects of the present invention include a composition comprising a compound of Formula (I) and Formula (II) wherein Q and Q^1 of substituents R_{12} and R_{13} are the same within a given compound and is
the C_{17} saturated chain of stearoic acid.

Another aspect of the present invention includes compounds of Formula (I) and Formula (II) wherein
W is preferably is selected from the group consisting of -$C_{0\text{-}4}$alkyl(R_1), -$C_{1\text{-}4}$alkyl(R_{1a}), -$C_{0\text{-}4}$alkyl-aryl(R_1,R_8), -$C_{0\text{-}4}$alkyl-heterocyclyl(R_1,R_8), -$C_{0\text{-}4}$alkoxy(R_1), -$C_{0\text{-}4}$alkoxy-aryl(R_1,R_8), and -$C_{0\text{-}4}$alkoxy-heterocyclyl(R_1,R_8);

R_1 is -N(R_4)(R_6), -heterocyclyl(R_8) or -heteroaryl(R_8);

R_{1a} is -C(R_4)(=N-R_4), -C(=N-R_4)-N(R_4)$_2$, -C(=N-R_4)-N(R_4)(R_6), -C(=N-R_4)-N(R_4)-C(=O)-R_4, -C(=N-R_4)-N(R_4)-C(=O)-N(R_4)$_2$, -C(=N-R_4)-N(R_4)-CO_2-R_4, -C(=N-R_4)-N(R_4)-SO_2-$C_{1\text{-}4}$alkyl(R_7) or -C(=N-R_4)-N(R_4)-SO_2-N(R_4)$_2$;

R_4 is hydrogen or -$C_{1\text{-}4}$alkyl(R_7);

R_5 is -C(=O)-R_4, -C(=O)-N(R_4)$_2$, -C(=O)-cycloalkyl(R_8), -C(=O)-heterocyclyl(R_8), -C(=O)-aryl(R_8), -C(=O)-heteroaryl(R_8), -C(=O)-N(R_4)-cycloalkyl(R_8),

-C(=O)-N(R_4)-aryl(R_8), -CO_2-R_4, -CO_2-cycloalkyl(R_8), -CO_2-aryl(R_8), -C(R_4)(=N-R_4), -C(=N-R_4)-N(R_4)$_2$, -C(=N-R_4)-N(R_4)(R_6), -C(=N-R_4)-N(R_4)-C(=O)-R_4, -C(=N-R_4)-N(R_4)-C(=O)-N(R_4)$_2$, -C(=N-R_4)-N(R_4)-CO_2-R_4, -C(=N-R_4)-N(R_4)-SO_2-C_{1-4}alkyl(R_7), -C(=N-R_4)-N(R_4)-SO_2-N(R_4)$_2$, -N(R_4)-C(R_4)(=N-R_4), -N(R_4)-C(=N-R_4)-N(R_4)$_2$, -N(R_4)-C(=N-R_4)-N(R_4)(R_6), -N(R_4)-C(=N-R_4)-N(R_4)-C(=O)-R_4, -N(R_4)-C(=N-R_4)-N(R_4)-C(=O)-N(R_4)$_2$, -N(R_4)-C(=N-R_4)-N(R_4)-CO_2-R_4, -N(R_4)-C(=N-R_4)-N(R_4)-SO_2-C_{1-4}alkyl(R_7), -N(R_4)-C(=N-R_4)-N(R_4)-SO_2-N(R_4)$_2$, -SO_2-C_{1-4}alkyl(R_7), -SO_2-N(R_4)$_2$, -SO_2-cycloalkyl(R_8) or -SO_2-aryl(R_8);

R_6 is -heterocyclyl(R_8) or -heteroaryl(R_8);

R_7 is one to two substituents independently selected from hydrogen, -C_{1-4}alkoxy(R_9), -NH_2, -NH-C_{1-4}alkyl(R_9), -N(C_{1-4}alkyl(R_9))$_2$, -C(=O)H, -C(=O)-C_{1-4}alkyl(R_9), -C(=O)-NH_2, -C(=O)-NH-C_{1-4}alkyl(R_9), -C(=O)-N(C_{1-4}alkyl(R_9))$_2$, -C(=O)-NH-aryl(R_{10}), -C(=O)-cycloalkyl(R_{10}), -C(=O)-heterocyclyl(R_{10}), -C(=O)-aryl(R_{10}), -C(=O)-heteroaryl(R_{10}), -CO_2H, -CO_2-C_{1-4}alkyl(R_9), -CO_2-aryl(R_{10}), -C(=NH)-NH_2, -SH, -S-C_{1-4}alkyl(R_9), -S-C_{1-4}alkyl-S-C_{1-4}alkyl(R_9), -S-C_{1-4}alkyl-C_{1-4}alkoxy(R_9), -S-C_{1-4}alkyl-NH-C_{1-4}alkyl(R_9), -SO_2-C_{1-4}alkyl(R_9), -SO_2-NH_2, -SO_2-NH-C_{1-4}alkyl(R_9), -SO_2-N(C_{1-4}alkyl(R_9))$_2$, -SO_2-aryl(R_{10}), cyano, (halo)$_{1-3}$, hydroxy, nitro, oxo, -cycloalkyl(R_{10}), -heterocyclyl(R_{10}), -aryl(R_{10}) or -heteroaryl(R_{10});

R_8 is one to four substituents independently selected from hydrogen, -C_{1-4}alkyl(R_9), -C(=O)H, -C(=O)-NH_2, -C(=O)-NH-C_{1-4}alkyl(R_9), -C(=O)-N(C_{1-4}alkyl(R_9))$_2$, -CO_2H, -CO_2-C_{1-4}alkyl(R_9) or -SO_2-NH_2 when attached to a nitrogen atom; and, wherein R_8 is one to four substituents independently selected from hydrogen, -C_{1-4}alkyl(R_9), -C_{1-4}alkoxy(R_9), -O-aryl(R_{10}), -C(=O)H, -C(=O)-NH_2, -C(=O)-NH-C_{1-4}alkyl(R_9), -C(=O)-N(C_{1-4}alkyl(R_9))$_2$, -CO_2H, -CO_2-C_{1-4}alkyl(R_9), -SO_2-NH_2, -NH_2, -NH-C_{1-4}alkyl(R_9), -N(C_{1-4}alkyl(R_9))$_2$, cyano, halo, hydroxy, nitro or oxo when attached to a carbon atom;

R_9 is hydrogen, $-C_{1-4}$alkoxy, $-NH_2$, $-NH-C_{1-4}$alkyl, $-N(C_{1-4}alkyl)_2$, $-C(=O)H$, $-C(=O)-NH_2$, $-C(=O)-NH-C_{1-4}$alkyl, $-C(=O)-N(C_{1-4}alkyl)_2$, $-CO_2H$, $-CO_2-C_{1-4}$alkyl, $-SO_2-C_{1-4}$alkyl, $-SO_2-NH_2$, $-SO_2-NH-C_{1-4}$alkyl, $-SO_2-N(C_{1-4}alkyl)_2$, cyano, $(halo)_{1-3}$, hydroxy, nitro or oxo;

R_{10} is one to four substituents independently selected from hydrogen, $-C_{1-4}$alkyl, $-C(=O)H$, $-C(=O)-C_{1-4}$alkyl, $-C(=O)-NH_2$, $-C(=O)-NH-C_{1-4}$alkyl, $-C(=O)-N(C_{1-4}alkyl)_2$, $-CO_2H$, $-CO_2-C_{1-4}$alkyl, $-SO_2-C_{1-4}$alkyl, $-SO_2-NH_2$, $-SO_2-NH-C_{1-4}$alkyl or $-SO_2-N(C_{1-4}alkyl)_2$ when attached to a nitrogen atom; and, wherein R_{10} is one to four substituents independently selected from hydrogen, $-C_{1-4}$alkyl, $-C_{1-4}$alkoxy, $-C(=O)H$, $-C(=O)-C_{1-4}$alkyl, $-C(=O)-NH_2$, $-C(=O)-NH-C_{1-4}$alkyl, $-C(=O)-N(C_{1-4}alkyl)_2$, $-CO_2H$, $-CO_2-C_{1-4}$alkyl, $-SO_2-C_{1-4}$alkyl, $-SO_2-NH_2$, $-SO_2-NH-C_{1-4}$alkyl, $-SO_2-N(C_{1-4}alkyl)_2$, $-NH_2$, $-NH-C_{1-4}$alkyl, $-N(C_{1-4}alkyl)_2$, cyano, halo, hydroxy, nitro or oxo when attached to a carbon atom;

R_{2a} is -cycloalkyl$(R_8)(R_{11})$, -heterocyclyl$(R_8)(R_{12})$, -aryl$(R_8)(R_{12})$ or -heteroaryl$(R_8)(R_{12})$;

q is 1, 2 or 3.

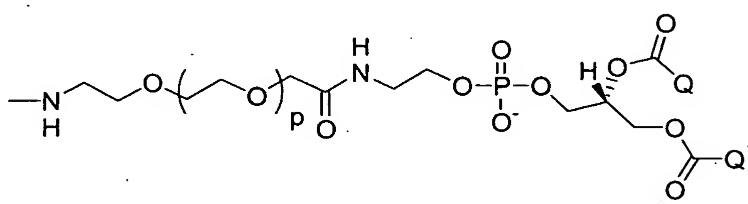
R_{11} is selected from the group consisting of $-C_{1-8}alkyl(R_{13})$, $-O-C_{1-8}alkyl(R_{13})$, $-NH-C_{1-8}alkyl(R_{13})$, $-S-C_{1-8}alkyl(R_{13})$, $-C(=O)C_{1-8}alkyl(R_{13})$, $-O-C(=O)C_{1-8}alkyl(R_{13})$, $-NH-C(=O)C_{1-8}alkyl(R_{13})$, $-C(=O)OC_{1-8}alkyl(R_{13})$, $-C(=O)NHC_{1-8}alkyl(R_{13})$, $-O-C(=O)OC_{1-8}alkyl(R_{13})$, $-O-C(=O)NHC_{1-8}alkyl(R_{13})$, $-O-C(=O)C_{1-8}alkylC(=O)(R_{13})$, $-NH-C(=O)C_{1-8}alkylC(=O)(R_{13})$, $-C(=O)OC_{1-8}alkylC(=O)(R_{13})$, $-O-C(=O)OC_{1-8}alkylC(=O)(R_{13})$, $-NH-C(=O)OC_{1-8}alkylC(=O)(R_{13})$, $-C(=O)NHC_{1-8}alkylC(=O)(R_{13})$, $-O-C(=O)NHC_{1-8}alkylC(=O)(R_{13})$, $-NH-C(=O)NHC_{1-8}alkylC(=O)(R_{13})$, $-SCH_2CH_2O(CH_2CH_2O)_rCH_2CH_2(R_{13})$, $-NHCH_2CH_2O(CH_2CH_2O)_rCH_2C(=O)(R_{13})$,

$-SO_2NHCH_2CH_2O(CH_2CH_2O)_rCH_2CH_2(R_{13})$, $-C(=O)CH_2O(CH_2CH_2O)_rCH_2C(=O)(R_{13})$, $-OC(=O)OCH_2CH_2O(CH_2CH_2O)_rCH_2C(=O)(R_{13})$, $-OC(=O)NHCH_2CH_2O(CH_2CH_2O)_rCH_2C(=O)(R_{13})$, $-NHC(=O)NHCH_2CH_2O(CH_2CH_2O)_rCH_2C(=O)(R_{13})$, and $-SO_2NHCH_2CH_2O(CH_2CH_2O)_rCH_2C(=O)(R_{13})$;

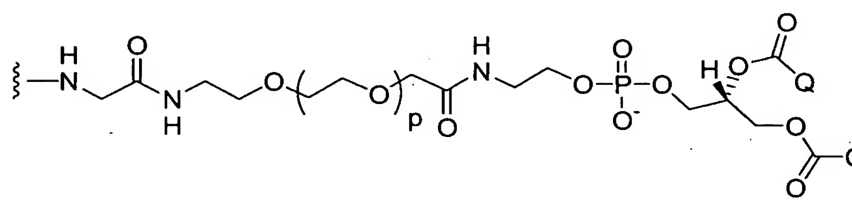
R_{12} is selected from the group consisting of $-C_{1-6}alkyl(R_{13})$, $-O-C_{1-6}alkyl(R_{13})$, $-NH-C_{1-4}alkyl(R_{13})$, $-S-C_{1-6}alkyl(R_{13})$, $-CH_2O-C_{1-6}alkyl(R_{13})$, $-CH_2NH-C_{1-6}alkyl(R_{13})$, $-CH_2S-C_{1-6}alkyl(R_{13})$, $-C(=O)C_{1-6}alkyl(R_{13})$, $-O-C(=O)C_{1-6}alkyl(R_{13})$, $-NH-C(=O)C_{1-8}alkyl(R_{13})$, $-CH_2O-C(=O)C_{1-8}alkyl(R_{13})$, $-CH_2NH-C(=O)C_{1-6}alkyl(R_{13})$, $-C(=O)OC_{1-6}alkyl(R_{13})$, $-C(=O)NHC_{1-6}alkyl(R_{13})$, $-O-C(=O)OC_{1-6}alkyl(R_{13})$, $-O-C(=O)NHC_{1-6}alkyl(R_{13})$, $-NH-C(=O)OC_{1-6}alkyl(R_{13})$, $-NH-C(=O)NHC_{1-6}alkyl(R_{13})$, $-NH-C(=O)C_{1-6}alkylC(=O)(R_{13})$, $-CH_2O-C(=O)C_{1-8}alkylC(=O)(R_{13})$, $-NH-C(=O)NHC_{1-8}alkylC(=O)(R_{13})$, $-CH_2O-C(=O)NHC_{1-8}alkylC(=O)(R_{13})$, $-CH_2NH-C(=O)NHC_{1-8}alkylC(=O)(R_{13})$, $-OCH_2CH_2O(CH_2CH_2O)_rCH_2CH_2(R_{13})$, $-NHCH_2CH_2O(CH_2CH_2O)_rCH_2CH_2(R_{13})$, $-SCH_2CH_2O(CH_2CH_2O)_rCH_2CH_2(R_{13})$, $-OCH_2CH_2O(CH_2CH_2O)_rCH_2C(=O)(R_{13})$, $-NHCH_2CH_2O(CH_2CH_2O)_rCH_2C(=O)(R_{13})$, $-OC(=O)NHCH_2CH_2O(CH_2CH_2O)_rCH_2CH_2(R_{13})$, $-NH(C=O)CH_2O(CH_2CH_2O)_rCH_2CH_2(R_{13})$, $-NHC(=O)OCH_2CH_2O(CH_2CH_2O)_rCH_2CH_2(R_{13})$, $-NHC(=O)NHCH_2CH_2O(CH_2CH_2O)_rCH_2CH_2(R_{13})$, $-SO_2CH_2CH_2O(CH_2CH_2O)_rCH_2CH_2(R_{13})$, $-SO_2NHCH_2CH_2O(CH_2CH_2O)_rCH_2CH_2(R_{13})$, $-CH_2OCH_2CH_2O(CH_2CH_2O)_rCH_2CH_2(R_{13})$, $-CH_2NHCH_2CH_2O(CH_2CH_2O)_rCH_2CH_2(R_{13})$,

$-CH_2SCH_2CH_2O(CH_2CH_2O)_rCH_2CH_2(R_{13})$,
$-CH_2OCH_2CH_2O(CH_2CH_2O)_rCH_2C(=O)(R_{13})$,
$-OC(=O)NHCH_2CH_2O(CH_2CH_2O)_rCH_2C(=O)(R_{13})$,
$-NH(C=O)CH_2O(CH_2CH_2O)_rCH_2C(=O)(R_{13})$,
$-NHC(=O)OCH_2CH_2O(CH_2CH_2O)_rCH_2C(=O)(R_{13})$,
$-NHC(=O)NHCH_2CH_2O(CH_2CH_2O)_rCH_2C(=O)(R_{13})$,
$-CH_2OC(=O)CH_2O(CH_2CH_2O)_rCH_2C(=O)(R_{13})$,
$-CH_2NH(C=O)CH_2O(CH_2CH_2O)_rCH_2C(=O)(R_{13})$,
$-CH_2NHC(=O)OCH_2CH_2O(CH_2CH_2O)_rCH_2C(=O)(R_{13})$, and
$-CH_2NHC(=O)NHCH_2CH_2O(CH_2CH_2O)_rCH_2C(=O)(R_{13})$;

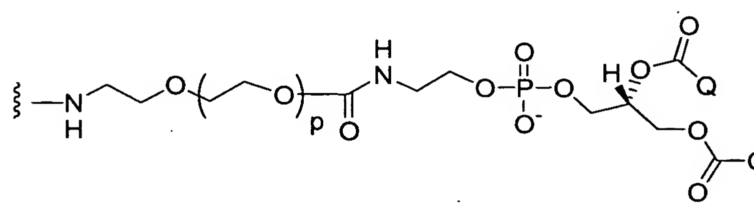
wherein when R_{11} or R_{12} terminates with a –C(=O)-, R_{13} is selected from the group consisting of



,

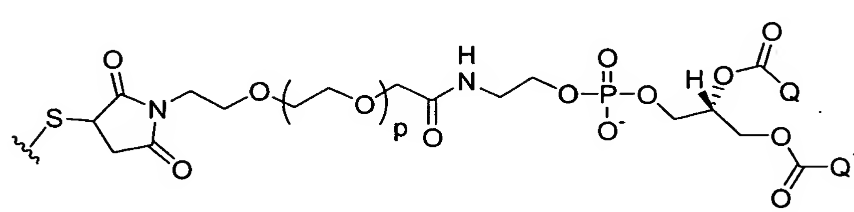


, and

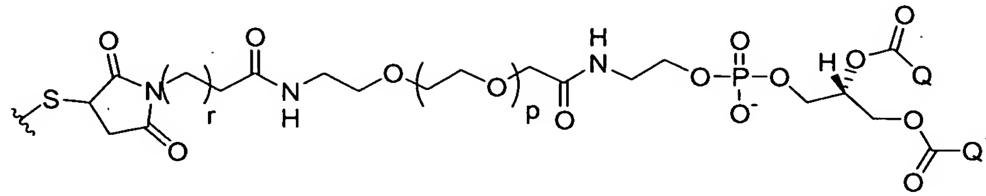


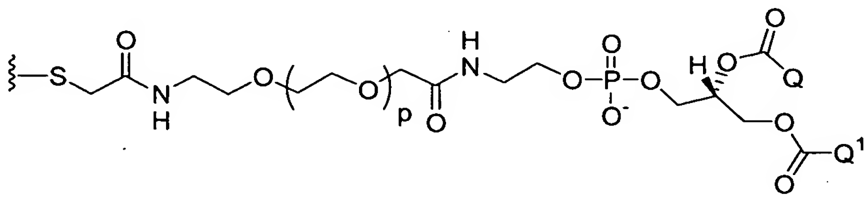
;

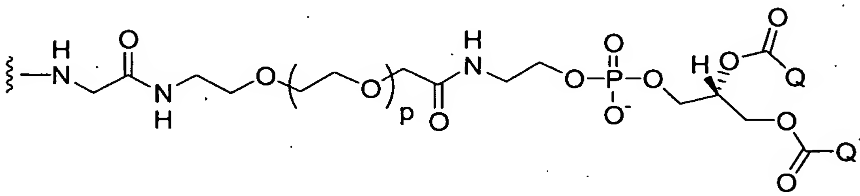
and when R_{11} or R_{12} does not terminate with a –C(=O)-, R_{13} is selected from the group consisting of

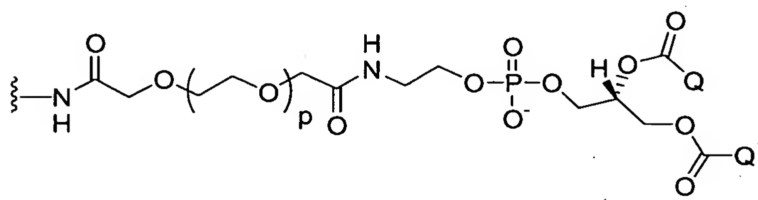


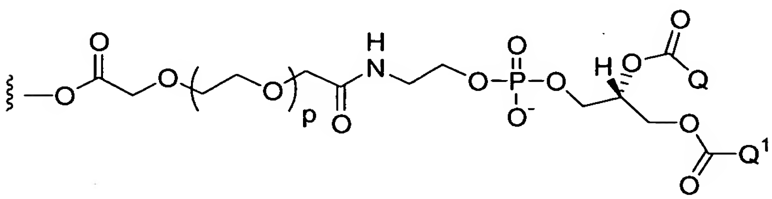
,

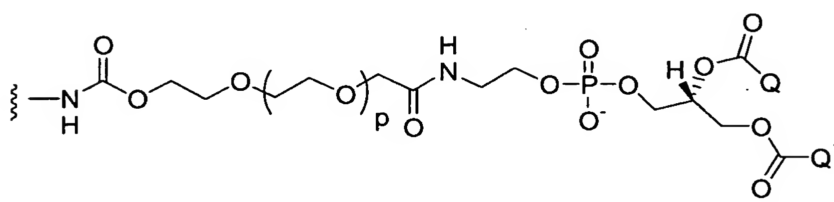

,

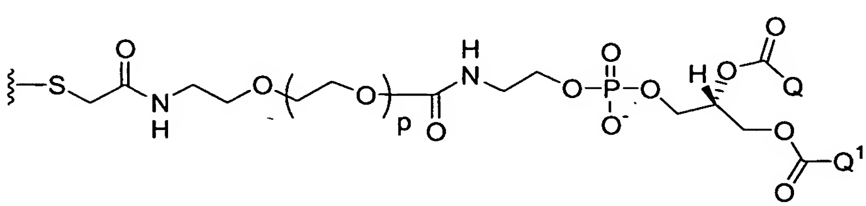

,

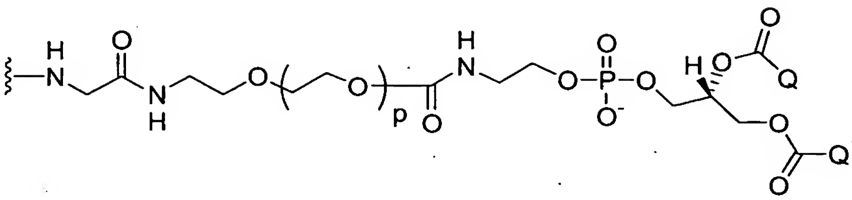

,


,

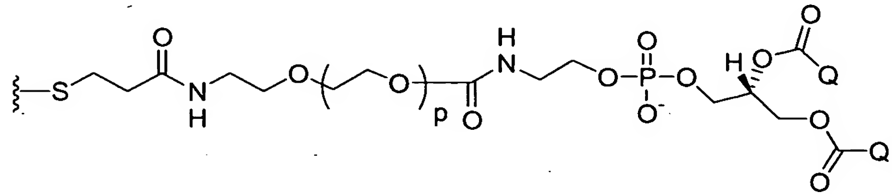

,


,

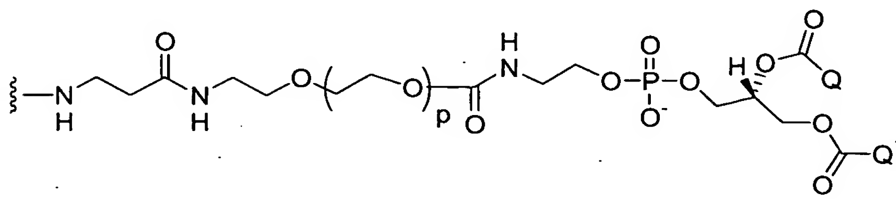

,



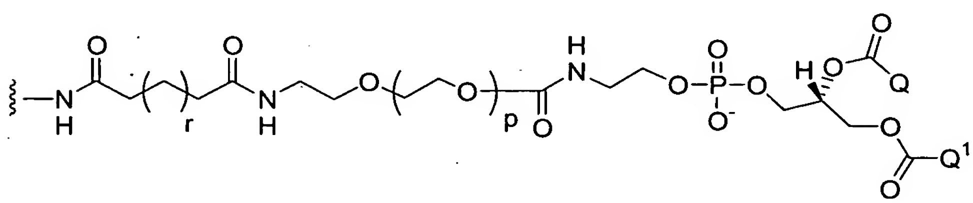
,



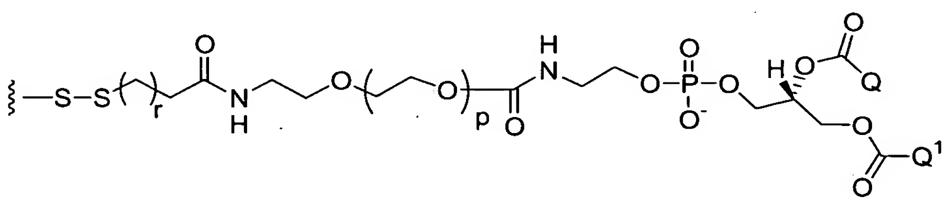
,



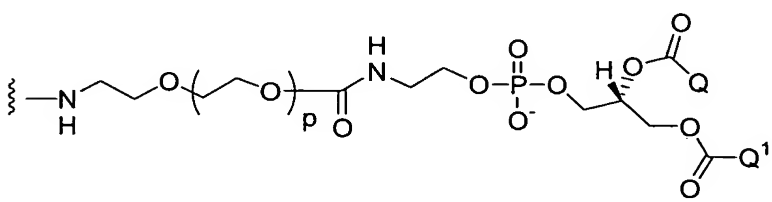
,



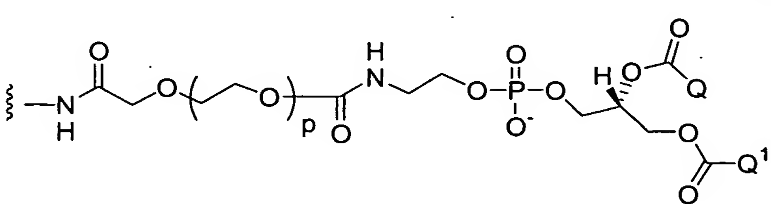
,



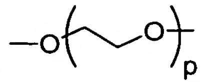
,



, and



;

said $-O-(CH_2CH_2O-)_p-$ or  of R_{12} and R_{13} is a polyethylene glycol (PEG) polymer ranging in molecular weight from 750 to 5000 daltons;

r is an integer from 0 to 8.

Q and Q^1 of substituents R_{12} and R_{13} are the same within a given compound and are selected from the group consisting of
the C_{11} saturated chain of lauric acid,
the C_{15} saturated chain of palmitoic acid,
the C_{17} saturated chain of stearoic acid,
the C_{17} mono-unsaturated chain of oleoic acid, and
the C_{17} di-unsaturated chain of linoleic acid;

Z is selected from the group consisting of hydroxy, $-NH_2$, -NH-C_{1-8}alkyl, -N(C_{1-8}alkyl)$_2$, -O-C_{1-8}alkyl, -O-C_{1-8}alkyl-OH, -O-C_{1-8}alkylC_{1-4}alkoxy, -O-C_{1-8}alkylcarbonylC_{1-4}alkyl, -O-C_{1-8}alkyl-CO_2H, -O-C_{1-8}alkyl-C(O)O-C_{1-6}alkyl, -O-C_{1-8}alkyl-O-C(O)C_{1-8}alkyl, -O-C_{1-8}alkyl-NH_2, -O-C_{1-8}alkyl-NH-C_{1-8}alkyl, -O-C_{1-8}alkyl-N(C_{1-8}alkyl)$_2$, –O-C_{1-8}alkylamide -O-C_{1-8}alkyl-C(O)-NH-C_{1-8}alkyl, -O-C_{1-8}alkyl-C(O)-N(C_{1-8}alkyl)$_2$ and
–NHC(O)C_{1-8}alkyl.

Aspects of the present invention include compounds of Formula (I) and Formula (II) wherein:

W is preferably -C_{0-4}alkyl(R_1) or -C_{0-4}alkyl-aryl(R_1,R_8);

R_1 is -N(R_4)(R_6), -dihydro-1*H*-pyrrolo[2,3-*b*]pyridinyl(R_8), -tetrahydropyrimidinyl(R_8), -tetrahydro-1,8-naphthyridinyl(R_8), -tetrahydro-1*H*-azepino[2,3-*b*]pyridinyl(R_8) or -pyridinyl(R_8);

R_{1a} is -C(R_4)(=N-R_4), -C(=N-R_4)-N(R_4)$_2$, -C(=N-R_4)-N(R_4)(R_6),

$-C(=N-R_4)-N(R_4)-C(=O)-R_4$, $-C(=N-R_4)-N(R_4)-C(=O)-N(R_4)_2$, $-C(=N-R_4)-N(R_4)-CO_2-R_4$, $-C(=N-R_4)-N(R_4)-SO_2-C_{1-4}alkyl(R_7)$ or $-C(=N-R_4)-N(R_4)-SO_2-N(R_4)_2$;

R_4 is hydrogen or $-C_{1-4}alkyl(R_7)$;

R_5 is $-C(=O)-R_4$, $-C(=O)-N(R_4)_2$, $-C(=O)$-cycloalkyl(R_8), $-C(=O)$-heterocyclyl(R_8), $-C(=O)$-aryl(R_8), $-C(=O)$-heteroaryl(R_8), $-C(=O)-N(R_4)$-cycloalkyl(R_8), $-C(=O)-N(R_4)$-aryl(R_8), $-CO_2-R_4$, $-CO_2$-cycloalkyl(R_8), $-CO_2$-aryl(R_8), $-C(R_4)(=N-R_4)$, $-C(=N-R_4)-N(R_4)_2$, $-C(=N-R_4)-N(R_4)(R_6)$, $-C(=N-R_4)-N(R_4)-C(=O)-R_4$, $-C(=N-R_4)-N(R_4)-C(=O)-N(R_4)_2$, $-C(=N-R_4)-N(R_4)-CO_2-R_4$, $-C(=N-R_4)-N(R_4)-SO_2-C_{1-4}alkyl(R_7)$, $-C(=N-R_4)-N(R_4)-SO_2-N(R_4)_2$, $-N(R_4)-C(R_4)(=N-R_4)$, $-N(R_4)-C(=N-R_4)-N(R_4)_2$, $-N(R_4)-C(=N-R_4)-N(R_4)(R_6)$, $-N(R_4)-C(=N-R_4)-N(R_4)-C(=O)-R_4$, $-N(R_4)-C(=N-R_4)-N(R_4)-C(=O)-N(R_4)_2$, $-N(R_4)-C(=N-R_4)-N(R_4)-CO_2-R_4$, $-N(R_4)-C(=N-R_4)-N(R_4)-SO_2-C_{1-4}alkyl(R_7)$, $-N(R_4)-C(=N-R_4)-N(R_4)-SO_2-N(R_4)_2$, $-SO_2-C_{1-4}alkyl(R_7)$, $-SO_2-N(R_4)_2$, $-SO_2$-cycloalkyl(R_8) or $-SO_2$-aryl(R_8).

R_6 is -heterocyclyl(R_8) or -heteroaryl(R_8);

R_7 is one to two substituents independently selected from hydrogen, $-C_{1-4}alkoxy(R_9)$, $-NH_2$, $-NH-C_{1-4}alkyl(R_9)$, $-N(C_{1-4}alkyl(R_9))_2$, $(halo)_{1-3}$, hydroxy or oxo;

R_8 is one to four substituents independently selected from hydrogen or $-C_{1-4}alkyl(R_9)$ when attached to a nitrogen atom; and, wherein R_8 is one to four substituents independently selected from hydrogen, $-C_{1-4}alkyl(R_9)$, $-C_{1-4}alkoxy(R_9)$, $-O$-aryl(R_{10}), $-NH_2$, $-NH-C_{1-4}alkyl(R_9)$, $-N(C_{1-4}alkyl(R_9))_2$, halo, hydroxy or oxo when attached to a carbon atom;

R_9 is hydrogen, $-C_{1-4}alkoxy$, $-NH_2$, $-NH-C_{1-4}alkyl$, $-N(C_{1-4}alkyl)_2$, $-C(=O)H$, $-CO_2H$, $-C(=O)-C_{1-4}alkoxy$, $(halo)_{1-3}$, hydroxy or oxo;

$(R_{10})_{1-4}$ is hydrogen, $-C_{1-4}$alkyl, $-C_{1-4}$alkoxy, -C(=O)H, $-C(=O)-C_{1-4}$alkyl, $-CO_2H$, $-CO_2-C_{1-4}$alkyl, $-NH_2$, $-NH-C_{1-4}$alkyl, $-N(C_{1-4}alkyl)_2$, halo, hydroxy, nitro or oxo when attached to a carbon atom;

R_{2a} is -cycloalkyl$(R_7)(R_{11})$, -heterocyclyl$(R_8)(R_{12})$, -phenyl$(R_8)(R_{12})$, -naphthalenyl$(R_8)(R_{12})$ or -heteroaryl$(R_8)(R_{12})$;

q is 1, 2 or 3;

R_{11} is selected from the group consisting of $-C_{1-8}alkyl(R_{13})$, $-O-C_{1-8}alkyl(R_{13})$, $-NH-C_{1-8}alkyl(R_{13})$, $-S-C_{1-8}alkyl(R_{13})$, $-C(=O)C_{1-8}alkyl(R_{13})$, $-O-C(=O)C_{1-8}alkyl(R_{13})$, $-NH-C(=O)C_{1-8}alkyl(R_{13})$, $-C(=O)OC_{1-8}alkyl(R_{13})$, $-C(=O)NHC_{1-8}alkyl(R_{13})$, $-O-C(=O)OC_{1-8}alkyl(R_{13})$, $-O-C(=O)NHC_{1-8}alkyl(R_{13})$, $-O-C(=O)C_{1-8}alkylC(=O)(R_{13})$, $-NH-C(=O)C_{1-8}alkylC(=O)(R_{13})$, $-C(=O)OC_{1-8}alkylC(=O)(R_{13})$, $-O-C(=O)OC_{1-8}alkylC(=O)(R_{13})$, $-NH-C(=O)OC_{1-8}alkylC(=O)(R_{13})$, $-C(=O)NHC_{1-8}alkylC(=O)(R_{13})$, $-O-C(=O)NHC_{1-8}alkylC(=O)(R_{13})$, and $-NH-C(=O)NHC_{1-8}alkylC(=O)(R_{13})$.

R_{12} is selected from the group consisting of
$-CH_2O-C_{1-6}alkyl(R_{13})$,
$-CH_2NH-C_{1-6}alkyl(R_{13})$, $-CH_2S-C_{1-6}alkyl(R_{13})$,
$-NH-C(=O)C_{1-8}alkyl(R_{13})$,
$-CH_2NH-C(=O)C_{1-6}alkyl(R_{13})$,
$-NH-C(=O)NHC_{1-6}alkyl(R_{13})$,
$-NH-C(=O)C_{1-6}alkylC(=O)(R_{13})$,
$-OCH_2CH_2O(CH_2CH_2O)_rCH_2CH_2(R_{13})$,
$-NHCH_2CH_2O(CH_2CH_2O)_rCH_2CH_2(R_{13})$,
$-OCH_2CH_2O(CH_2CH_2O)_rCH_2C(=O)(R_{13})$,
$-NH(C=O)CH_2O(CH_2CH_2O)_rCH_2CH_2(R_{13})$,
$-CH_2OCH_2CH_2O(CH_2CH_2O)_rCH_2CH_2(R_{13})$,

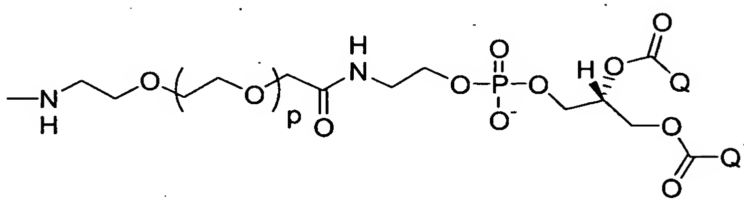
$-CH_2NHCH_2CH_2O(CH_2CH_2O)_rCH_2CH_2(R_{13})$,

$-CH_2SCH_2CH_2O(CH_2CH_2O)_rCH_2CH_2(R_{13})$,

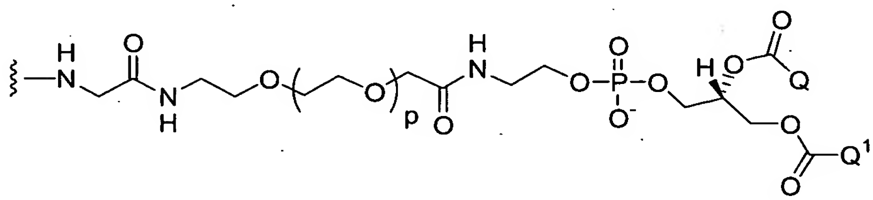
$-NH(C{=}O)CH_2O(CH_2CH_2O)_rCH_2C({=}O)(R_{13})$, and

$-CH_2NH(C{=}O)CH_2O(CH_2CH_2O)_rCH_2C({=}O)(R_{13})$;

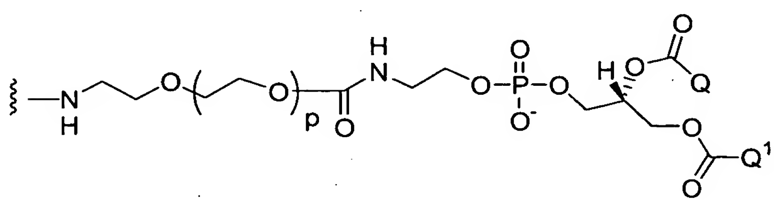
wherein when R_{11} or R_{12} terminates with a $-C(=O)-$, R_{13} is selected from the group consisting of



,

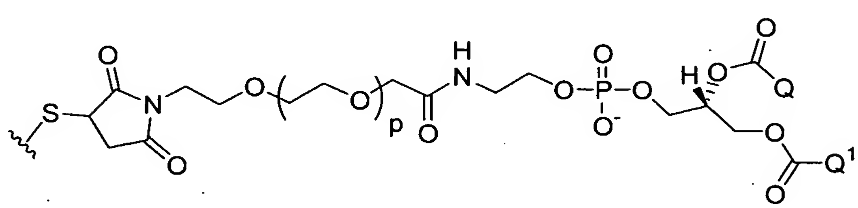


, and

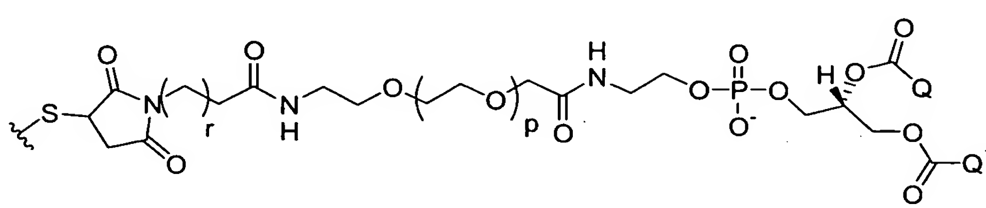


;

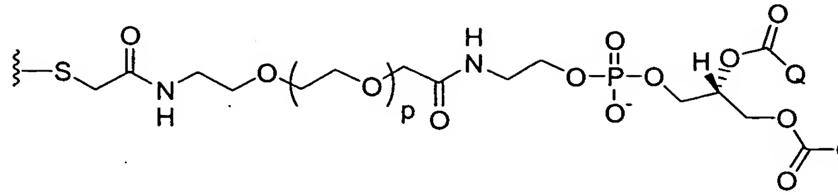
and when R_{11} or R_{12} does not terminate with a $-C(=O)-$, R_{13} is selected from the group consisting of



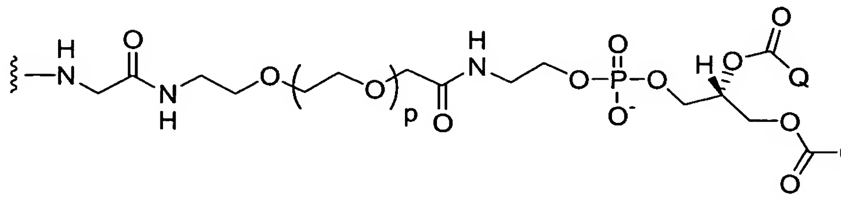
,



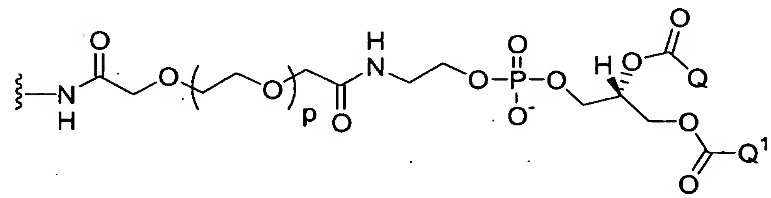
,



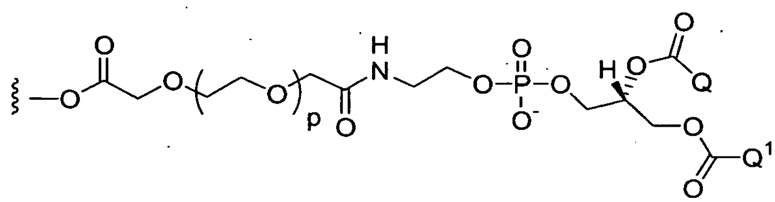
,



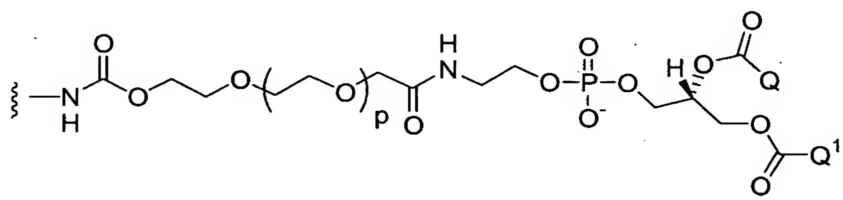
,



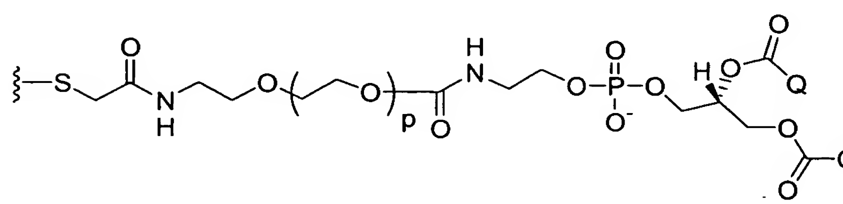
,



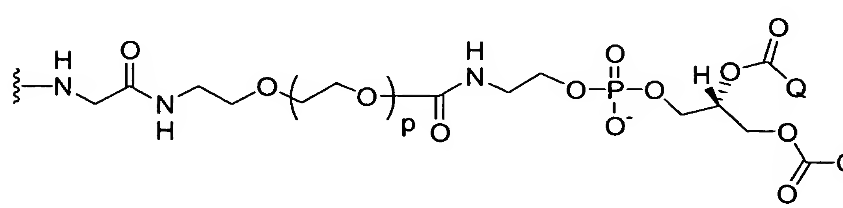
,



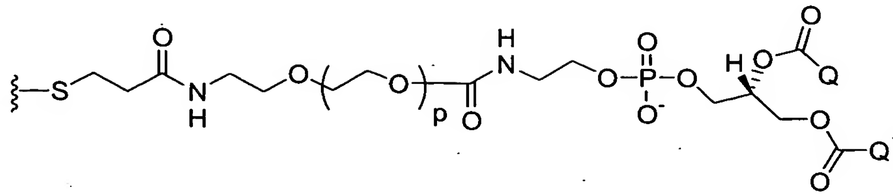
,

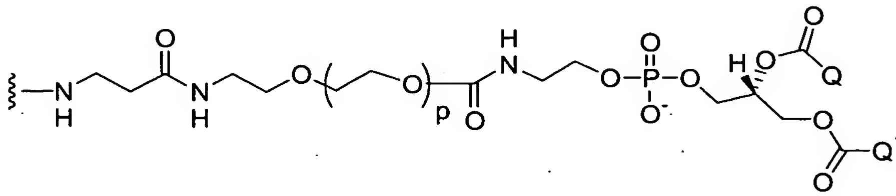


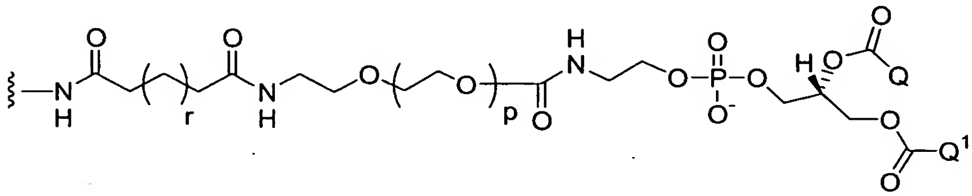
,

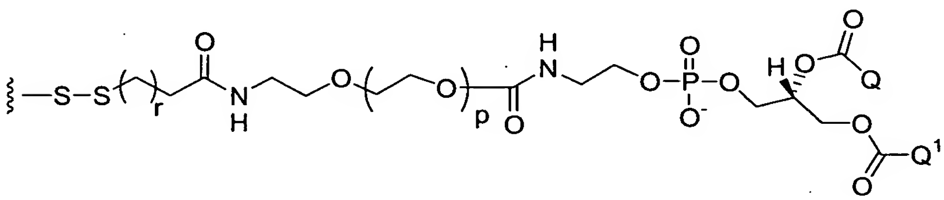


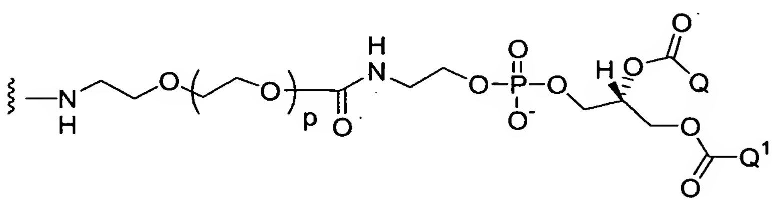
,

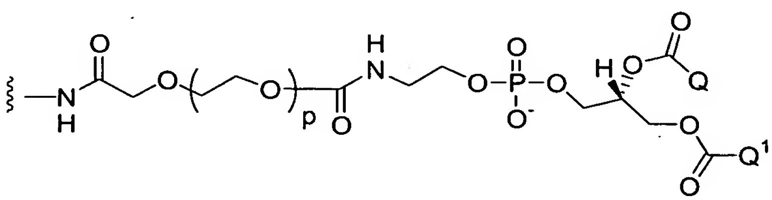

,

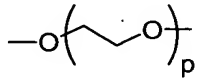

,


,


,


, and


.

wherein said $–O-(CH_2CH_2O-)_p-$ or  of R_{12} and R_{13} is a polyethylene glycol (PEG) polymer ranging in molecular weight from 2000 to 5000 daltons.

r is an integer from 0 to 8.

Q and Q[1] of substituents R_{12} and R_{13} are the same within a given compound and are selected from the group consisting of
the C_{15} saturated chain of palmitoic acid,
the C_{17} saturated chain of stearoic acid, and
the C_{17} mono-unsaturated chain of oleoic acid.

Z is selected from the group consisting of hydroxy, $-NH_2$, $-NH-C_{1-8}$alkyl, $-N(C_{1-8}alkyl)_2$, $-O-C_{1-8}$alkyl, $-O-C_{1-8}$alkyl-OH, $-O-C_{1-8}alkylC_{1-4}$alkoxy, $-O-C_{1-8}alkylcarbonylC_{1-4}$alkyl, $-O-C_{1-8}alkyl-CO_2H$, $-O-C_{1-8}alkyl-C(O)O-C_{1-6}$alkyl, $-O-C_{1-8}alkyl-O-C(O)C_{1-8}$alkyl, $-O-C_{1-8}alkyl-NH_2$, $-O-C_{1-8}alkyl-NH-C_{1-8}$alkyl, $-O-C_{1-8}alkyl-N(C_{1-8}alkyl)_2$, $–O-C_{1-8}$alkylamide $-O-C_{1-8}alkyl-C(O)-NH-C_{1-8}$alkyl, $-O-C_{1-8}alkyl-C(O)-N(C_{1-8}alkyl)_2$ and
$–NHC(O)C_{1-8}$alkyl.

Another aspect of the present invention includes compounds of Formula (I) and Formula (II) wherein:
W is preferably $-C_{0-4}alkyl(R_1)$ or $-C_{0-4}alkyl-phenyl(R_1,R_8)$;

R_1 is $-N(R_4)(R_6)$, -tetrahydropyrimidinyl(R_8) or -tetrahydro-1,8-naphthyridinyl(R_8);

R_{1a} is $-C(R_4)(=N-R_4)$, $-C(=N-R_4)-N(R_4)_2$, $-C(=N-R_4)-N(R_4)(R_6)$, $-C(=N-R_4)-N(R_4)-C(=O)-R_4$, $-C(=N-R_4)-N(R_4)-C(=O)-N(R_4)_2$, $-C(=N-R_4)-N(R_4)-CO_2-R_4$, $-C(=N-R_4)-N(R_4)-SO_2-C_{1-4}alkyl(R_7)$ or $-C(=N-R_4)-N(R_4)-SO_2-N(R_4)_2$;

R_4 is hydrogen;

R_5 is $-C(=O)-R_4$, $-C(=O)-N(R_4)_2$, $-CO_2-R_4$, $-C(R_4)(=N-R_4)$, $-C(=N-R_4)-N(R_4)_2$, $-C(=N-R_4)-N(R_4)(R_6)$, $-N(R_4)-C(R_4)(=N-R_4)$, $-N(R_4)-C(=N-R_4)-N(R_4)_2$, $-N(R_4)-C(=N-R_4)-N(R_4)(R_6)$, $-SO_2-C_{1-4}alkyl(R_7)$ or $-SO_2-N(R_4)_2$;

R_6 is -dihydroimidazolyl(R_8), -tetrahydropyridinyl(R_8), -tetrahydropyrimidinyl(R_8) or

-pyridinyl(R_8);

R_7 is hydrogen;

R_8 is one to four substituents independently selected from hydrogen or -C_{1-4}alkyl(R_9) when attached to a nitrogen atom; and, wherein R_8 is one to four substituents independently selected from hydrogen, -C_{1-4}alkyl(R_9), -C_{1-4}alkoxy(R_9) -O-aryl(R_{10}) or hydroxy when attached to a carbon atom;

R_9 is hydrogen, -C_{1-4}alkoxy, -NH_2, -NH-C_{1-4}alkyl, -N(C_{1-4}alkyl)$_2$, (halo)$_{1-3}$ or hydroxy;

R_{10} is hydrogen;

R_{2a} is -tetrahydropyrimidinyl(R_8)(R_{12}) , -1,3-benzodioxolyl(R_8)(R_{12}), -dihydrobenzofuranyl(R_8)(R_{12}), -tetrahydroquinolinyl(R_8)(R_{12}), -phenyl(R_8)(R_{12}), -naphthalenyl(R_8)(R_{12}), -pyridinyl(R_8)(R_{12}), -pyrimidinyl(R_8)(R_{12}) or -quinolinyl(R_8)(R_{12});

q is 1 or 2;

R_{12} is selected from the group consisting of

-CH_2-O-(CH_2)$_4$(R_{13})-,

-CH_2-NH-(CH_2)$_4$(R_{13})-,

-CH_2-S-(CH_2)$_4$(R_{13})-,

-CH_2-O-(CH_2)$_6$(R_{13})-,

-CH_2-NH-(CH_2)$_6$(R_{13})-,

-CH_2-S-(CH_2)$_6$(R_{13})-,

-NH-C(=O)-(CH_2)$_4$(R_{13})-,

-NH-C(=O)-(CH_2)$_7$(R_{13})-,

-NH-C(=O)NH-(CH_2)$_3$(R_{13})-,

-NH-C(=O)NH-(CH_2)$_6$(R_{13})-,

-CH_2NH-C(=O)NH-$(CH_2)_2(R_{13})$-,

-CH_2NH-C(=O)NH-$(CH_2)_5(R_{13})$-,

-NHC(=O)-$(CH_2)_2$-C(=O)(R_{13})-,

-NHC(=O)-$(CH_2)_3$-C(=O)(R_{13})-,

-NHC(=O)-$(CH_2)_4$-C(=O)(R_{13})-,

-$OCH_2CH_2OCH_2CH_2(R_{13})$-,

-$NHCH_2CH_2OCH_2CH_2(R_{13})$-,

-$OCH_2CH_2OCH_2CH_2OCH_2CH_2(R_{13})$-,

-$NHCH_2CH_2OCH_2CH_2OCH_2CH_2(R_{13})$-,

-$OCH_2CH_2OCH_2C$(=O)(R_{13})-,

-$OCH_2CH_2OCH_2CH_2OCH_2C$(=O)(R_{13})-,

-NHC(=O)$CH_2OCH_2CH_2(R_{13})$-,

-NHC(=O)$CH_2OCH_2CH_2OCH_2CH_2(R_{13})$-,

-$CH_2OCH_2CH_2OCH_2CH_2(R_{13})$-,

-$CH_2NHCH_2CH_2OCH_2CH_2(R_{13})$-,

-$CH_2SCH_2CH_2OCH_2CH_2(R_{13})$-,

-$CH_2OCH_2CH_2OCH_2CH_2OCH_2CH_2(R_{13})$-,

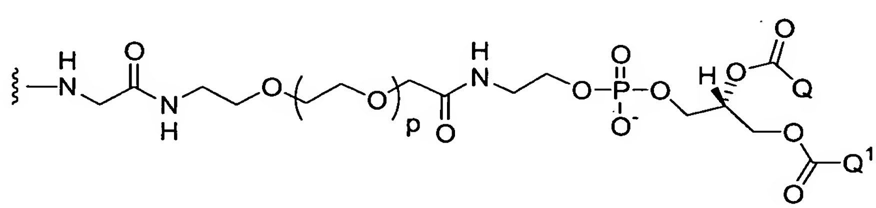
-$CH_2NHCH_2CH_2OCH_2CH_2OCH_2CH_2(R_{13})$-,

-$CH_2SCH_2CH_2OCH_2CH_2OCH_2CH_2(R_{13})$-,

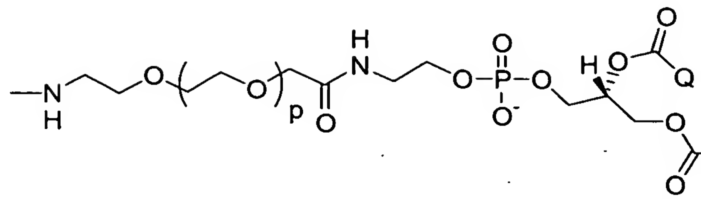
-CH_2NHC(=O)CH_2OCH_2C(=O)(R_{13})-, and

-NHC(=O)CH_2OCH_2C(=O)(R_{13})-;

wherein when R_{11} or R_{12} terminates with a –C(=O)-, R_{13} is selected from the group consisting of

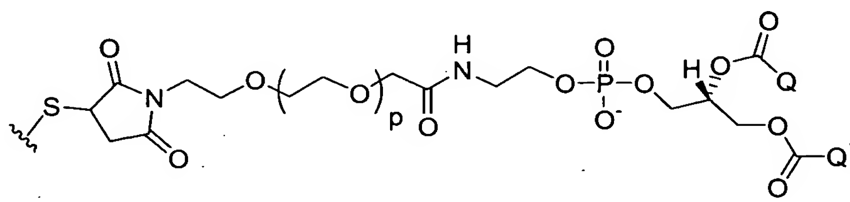


and

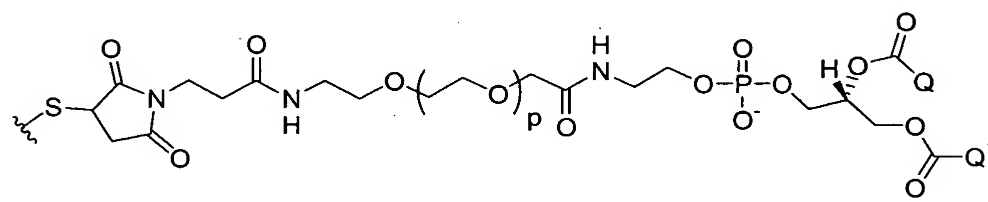


;

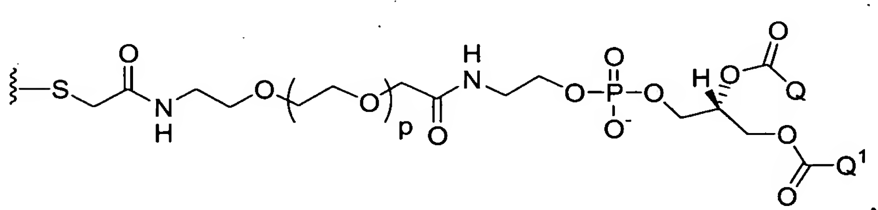
and when R_{11} or R_{12} does not terminate with a –C(=O)-, R_{13} is selected from the group consisting of



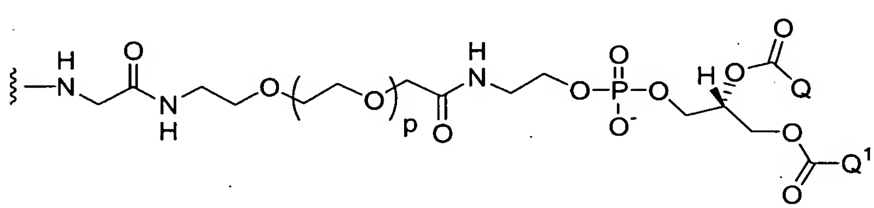
,



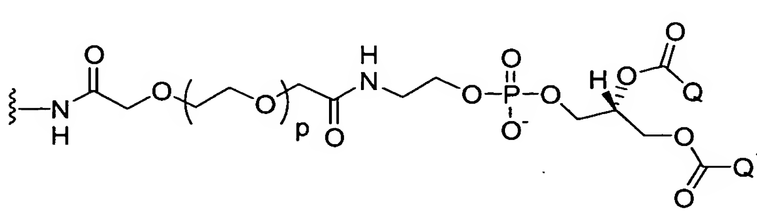
,



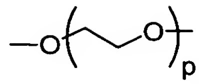
,



, and



;

wherein said $-O-(CH_2CH_2O-)_p-$ or  of R_{12} and R_{13} is a polyethylene glycol (PEG) polymer selected from 2000 (PEG 2000), 3400 (PEG 3400), or 5000 (PEG 5000) Daltons;

r is an integer from 0 to 8;

Q and Q^1 of substituents R_{12} and R_{13} are the same within a given compound and is the C_{17} saturated chain of stearoic acid;

Z is selected from the group consisting of hydroxy, $-NH_2$, $-NH-C_{1-8}$alkyl, $-N(C_{1-8}alkyl)_2$, $-O-C_{1-8}$alkyl, $-O-C_{1-8}$alkyl-OH, $-O-C_{1-8}$alkylC_{1-4}alkoxy, $-O-C_{1-8}$alkylcarbonylC_{1-4}alkyl, $-O-C_{1-8}$alkyl-CO_2H, $-O-C_{1-8}$alkyl-C(O)O-C_{1-6}alkyl, $-O-C_{1-8}$alkyl-O-C(O)C_{1-8}alkyl, $-O-C_{1-8}$alkyl-NH_2, $-O-C_{1-8}$alkyl-NH-C_{1-8}alkyl, $-O-C_{1-8}$alkyl-$N(C_{1-8}alkyl)_2$, $-O-C_{1-8}$alkylamide $-O-C_{1-8}$alkyl-C(O)-NH-C_{1-8}alkyl, $-O-C_{1-8}$alkyl-C(O)-$N(C_{1-8}alkyl)_2$ and

$-NHC(O)C_{1-8}$alkyl.

3. Liposomes

In a further aspect of the present invention is providing targeted liposomes.

Another aspect of the present invention includes a therapeutic liposome composition sensitized to a target cell, comprising

(i) a liposomal composition composed of pre-formed liposomes having an entrapped therapeutic agent; and

(ii) a plurality of conjugates, each conjugate composed of

(a) a lipid having a polar head group and a hydrophobic tail, (b) a hydrophilic polymer having a proximal end and a distal end, where the polymer is attached at its proximal end to the head group of the lipid, and (c) a targeting ligand attached to the distal end of the polymer. The therapeutic, target-cell sensitized liposome composition is formed by combining the liposomal composition with a conjugate selected from the plurality of conjugates.

Targeted liposomes, when administered systemically, are useful for carrying therapeutic agents to target cells. An advantage of targeted liposomes is that they may be directed to a specific region of diseased cells while avoiding exposure of normal tissues to the chemotherapeutic agent. In particular, stable long circulating liposomes (LCLs) are formulated with a coat of flexible, water soluble polymeric chains which prevent the uptake of the liposomes by the mononuclear phagocyte system, particularly the liver and spleen. Often an extended lifetime is necessary in order for the liposomes to reach their desired target region or cell from the site of injection.

To date, applications of targeted liposomes include the following: long-circulating, polyethylene glycol-grafted immunoliposomes (Allen, T.M. et al. Journal of Controlled Release, 91, (2003) 115-122); RGD-peptides coupled to the distal end of poly(ethylene glycol)-coated long-circulating liposomes (Storm, et al. Journal of Controlled Release, 39, (1996) 153-161).

Efforts have focused on ways to achieve site specific delivery of long-circulating liposomes. In one approach, targeting ligands, such as are described herein, are attached to the liposomes' surfaces. This approach, where the targeting ligand is bound to the polar head group residues of liposomal lipid components, results in interference by the surface-grafted polymer chains, inhibiting the interaction between the bound ligand and its intended target (Klibanov, A. L., et al., Biochim. Biophys. Acta., 1062:142-148 (1991); Hansen, C. B., et al., Biochim. Biophys. Acta, 1239:133-144 (1995)).

In another approach, the targeting ligand is attached to the free ends of the polymer chains forming the surface coat on the liposomes (Allen. T. M., et al., Biochim. Biophys. Acta, 1237:99-108 (1995); Blume, G. et al., Biochim. Biophys. Acta, 1149:180-184 (1993)). Two approaches have been described for preparing a liposome having a targeting ligand attached to the distal end of the surface polymer chains. One approach involves preparation of lipid vesicles which include an end-functionalized lipid-polymer derivative; that is, a lipid-polymer conjugate where the free polymer end is reactive or "activated". Such an activated conjugate is included in the liposome composition and the

activated polymer ends are reacted with a targeting ligand after liposome formation. The disadvantage to this approach is the difficulty in reacting all of the activated ends with a ligand. The approach also requires a subsequent step for separation of the unreacted ligand from the liposome composition.

In another approach, the lipid-polymer-ligand conjugate is included in the lipid composition at the time of liposome formation. This approach has the disadvantage that some of the valuable ligand faces the inner aqueous compartment of the liposome and is unavailable for interaction with the intended target.

3.A Liposome Definitions and Nomenclature

Unless otherwise noted, the term **"incubating"** refers to conditions of time, temperature and liposome lipid composition which allow for penetration and entry of a selected component, such as a lipid or lipid conjugate, into the lipid bilayer of a liposome.

Unless otherwise noted, the term **"pre-formed liposomes"** refers to intact, previously formed unilamellar or multilamellar lipid vesicles.

Unless otherwise noted, the term **"sensitized to a cell"** or **"target-cell sensitized"** refers to a liposome which includes a ligand or affinity moiety covalently bound to the liposome and having binding affinity for a receptor expressed on a particular cell.

Unless otherwise noted, the term **"therapeutic liposome composition"** refers to liposomes which include a therapeutic agent entrapped in the aqueous spaces of the liposomes or in the lipid bilayers of the liposomes.

Unless otherwise noted, the term **"vesicle-forming lipid"** refers to any lipid capable of forming part of a stable micelle or liposome composition and typically

including one or two hydrophobic, hydrocarbon chains or a steroid group and may contain a chemically reactive group, such as an amine, acid, ester, aldehyde or alcohol, at its polar head group.

3.B Targeted Liposomes

Liposomes are spherical vesicles comprised of concentrically ordered lipid bilayers that encapsulate an aqueous phase. Liposomes serve as a delivery vehicle for therapeutic agents contained in the aqueous phase or in the lipid bilayers. Delivery of drugs in liposome-entrapped form can provide a variety of advantages, depending on the drug, including, for example, a decreased drug toxicity, altered pharmacokinetics, or improved drug solubility. Liposomes when formulated to include a surface coating of hydrophilic polymer chains, so-called Stealth® or long-circulating liposomes, offer the further advantage of a long blood circulation lifetime, due in part to reduced removal of the liposomes by the mononuclear phagocyte system. Often an extended lifetime is necessary in order for the liposomes to reach their desired target region or cell from the site of injection.

Targeted liposomes, also referred to as immunoliposomes, have targeting ligands or affinity moieties attached to the surface of the liposomes. When administered systemically targeted liposomes are delivery the entrapped therapeutic agent to a target tissue, region or, cell. Because targeted liposomes are directed to a specific region or cell, healthy tissue is not exposed to the therapeutic agent. Such targeting ligands can be attached directly to the liposomes' surfaces by covalent coupling of the targeting ligand to the polar head group residues of liposomal lipid components (see, for example, U.S. Patent No. 5,013,556). This approach, however, is suitable primarily for liposomes that lack surface-bound polymer chains, as the polymer chains interfere with interaction between the targeting ligand and its intended target (Klibanov, A. L., et al., Biochim. Biophys. Acta., 1062:142-148 (1991); Hansen, C. B., et al., Biochim. Biophys. Acta, 1239:133-144 (1995)).

Alternatively, the targeting ligands can be attached to the free ends of the polymer

chains forming the surface coat on the liposomes (Allen. T. M., et al., Biochim. Biophys. Acta, 1237:99-108 (1995); Blume, G. et al., Biochim. Biophys. Acta, 1149:180-184 (1993)). In this approach, the targeting ligand is exposed and readily available for interaction with the intended target.

Accordingly, in another aspect, the invention includes a liposome composition comprised of liposomes that include a piperidinoyl carboxylic acid compound as a targeting ligand. The piperidinoyl carboxylic acid compound is incorporated into the liposomes in the form of a lipid-polymer-compound conjugate, also referred to herein as a lipid-polymer-ligand conjugate. As noted above, the piperidinoyl carboxylic acid compounds act as $\alpha_V\beta_3$, $\alpha_V\beta_5$, and/or $\alpha_V\beta_6$ integrin receptor antagonists and target the liposomes to cells that express one or more of these receptors. The following sections describe the liposome components, including the liposome lipids and therapeutic agents, preparation of liposomes bearing a targeting ligand, and methods of using the liposomal composition for treatment of disorders characterized by cellular expression of $\alpha_V\beta_3$, $\alpha_V\beta_5$, and/or $\alpha_V\beta_6$ integrin receptors.

3.C. Liposome Lipid Components

Liposomes suitable for use in the composition of the present invention include those composed primarily of vesicle-forming lipids. Such a vesicle-forming lipid is one which can form spontaneously into bilayer vesicles in water, as exemplified by the phospholipids, with its hydrophobic moiety in contact with the interior, hydrophobic region of the bilayer membrane, and its head group moiety oriented toward the exterior, polar surface of the membrane. Lipids capable of stable incorporation into lipid bilayers, such as cholesterol and its various analoges, can also be used in the liposomes.

The vesicle-forming lipids are preferably lipids having two hydrocarbon chains, typically acyl chains, and a head group, either polar or nonpolar. There are a variety of synthetic vesicle-forming lipids and naturally-occurring vesicle-forming lipids, including the phospholipids, such as phosphatidylcholine, phosphatidylethanolamine, phosphatidic acid, phosphatidylinositol, and sphingomyelin, where the two hydrocarbon chains are

typically between about 14-22 carbon atoms in length, and have varying degrees of unsaturation. The above-described lipids and phospholipids whose acyl chains have varying degrees of saturation can be obtained commercially or prepared according to published methods. Other suitable lipids include glycolipids, cerebrosides and sterols, such as cholesterol.

Cationic lipids are also suitable for use in the liposomes of the invention, where the cationic lipid can be included as a minor component of the lipid composition or as a major or sole component. Such cationic lipids typically have a lipophilic moiety, such as a sterol, an acyl or diacyl chain, and where the lipid has an overall net positive charge. Preferably, the head group of the lipid carries the positive charge. Exemplary cationic lipids include 1,2-dioleyloxy-3-(trimethylamino) propane (DOTAP); N-[1-(2,3,-ditetradecyloxy)propyl]-N,N-dimethyl-N-hydroxyethylammonium bromide (DMRIE); N-[1-(2,3,-dioleyloxy)propyl]-N,N-dimethyl-N-hydroxy ethylammonium bromide (DORIE); N-[1-(2,3-dioleyloxy) propyl]-N,N,N-trimethylammonium chloride (DOTMA); 3 [N-(N',N'-dimethylaminoethane) carbamoly] cholesterol (DC-Chol); and dimethyldioctadecylammonium (DDAB). The cationic vesicle-forming lipid may also be a neutral lipid, such as dioleoylphosphatidyl ethanolamine (DOPE) or an amphipathic lipid, such as a phospholipid, derivatized with a cationic lipid, such as polylysine or other polyamine lipids. For example, the neutral lipid (DOPE) can be derivatized with polylysine to form a cationic lipid.

The vesicle-forming lipid can be selected to achieve a specified degree of fluidity or rigidity, to control the stability of the liposome in serum, to control the conditions effective for insertion of the targeting conjugate, as will be described, and/or to control the rate of release of the entrapped agent in the liposome. Liposomes having a more rigid lipid bilayer, or a liquid crystalline bilayer, are achieved by incorporation of a relatively rigid lipid, e.g., a lipid having a relatively high phase transition temperature, e.g., up to 60°C. Rigid, i.e., saturated, lipids contribute to greater membrane rigidity in the lipid bilayer. Other lipid components, such as cholesterol, are also known to contribute to membrane rigidity in lipid bilayer structures.

On the other hand, lipid fluidity is achieved by incorporation of a relatively fluid lipid, typically one having a lipid phase with a relatively low liquid to liquid-crystalline phase transition temperature, e.g., at or below room temperature.

The liposomes also include a vesicle-forming lipid derivatized with a hydrophilic polymer. As has been described, for example in U.S. Pat. No. 5,013,556, including such a derivatized lipid in the liposome composition forms a surface coating of hydrophilic polymer chains around the liposome. The surface coating of hydrophilic polymer chains is effective to increase the in vivo blood circulation lifetime of the liposomes when compared to liposomes lacking such a coating.

Vesicle-forming lipids suitable for derivatization with a hydrophilic polymer include any of those lipids listed above, and, in particular phospholipids, such as distearoyl phosphatidylethanolamine (DSPE).

Hydrophilic polymers suitable for derivatization with a vesicle-forming lipid include polyvinylpyrrolidone, polyvinylmethylether, polymethyloxazoline, polyethyloxazoline, polyhydroxypropyloxazoline, polyhydroxypropylmethacrylamide, polymethacrylamide, polydimethylacrylamide, polyhydroxypropylmethacrylate, polyhydroxyethylacrylate, hydroxymethylcellulose, hydroxyethylcellulose, polyethyleneglycol, polyaspartamide and hydrophilic peptide sequences. The polymers may be employed as homopolymers or as block or random copolymers.

A preferred hydrophilic polymer chain is polyethyleneglycol (PEG), preferably as a PEG chain having a molecular weight between 500-10,000 daltons, more preferably between 750-10,000 daltons, still more preferably between 750-5000 daltons. Methoxy or ethoxy-capped analogues of PEG are also preferred hydrophilic polymers, commercially available in a variety of polymer sizes, e.g., 120-20,000 daltons.

Preparation of vesicle-forming lipids derivatized with hydrophilic polymers has been described, for example in U.S. Patent No. 5,395,619. Preparation of liposomes including such derivatized lipids has also been described, where typically between 1-20

mole percent of such a derivatized lipid is included in the liposome formulation (see, for example, U.S. Patent No. 5,013,556).

3.D. Liposome Preparation

Various approaches have been described for preparing liposomes having a targeting ligand attached to the distal end of liposome-attached polymer chains. One approach involves preparation of lipid vesicles which include an end-functionalized lipid-polymer derivative; that is, a lipid-polymer conjugate where the free polymer end is reactive or "activated" (see, for example, U.S. Patent Nos. 6,326,353 and 6,132,763). Such an activated conjugate is included in the liposome composition and the activated polymer ends are reacted with a targeting ligand after liposome formation. In another approach, the lipid-polymer-ligand conjugate is included in the lipid composition at the time of liposome formation (see, for example, U.S. Patent Nos. 6,224,903, 5,620,689). In yet another approach, a micellar solution of the lipid-polymer-ligand conjugate is incubated with a suspension of liposomes and the lipid-polymer-ligand conjugate is inserted into the pre-formed liposomes (see, for example, U.S. Patent Nos. 6,056,973, 6,316,024).

Liposomes carrying an entrapped agent and bearing surface-bound targeting ligands, i.e., targeted, therapeutic liposomes, are prepared by any of these approaches. A preferred method of preparation is the insertion method, where pre-formed liposomes and are incubated with the targeting conjugate to achieve insertion of the targeting conjugate into the liposomal bilayers. In this approach, liposomes are prepared by a variety of techniques, such as those detailed in Szoka, F., Jr., *et al., Ann. Rev. Biophys. Bioeng.*, 9:467 (1980), and specific examples of liposomes prepared in support of the present invention will be described below. Typically, the liposomes are multilamellar vesicles (MLVs), which can be formed by simple lipid-film hydration techniques. In this procedure, a mixture of liposome-forming lipids of the type detailed above dissolved in a suitable organic solvent is evaporated in a vessel to form a thin film, which is then covered by an aqueous medium. The lipid film hydrates to form MLVs, typically with sizes between about 0.1 to 10 microns.

The liposomes can include a vesicle-forming lipid derivatized with a hydrophilic polymer to form a surface coating of hydrophilic polymer chains on the liposomes surface. Addition of a lipid-polymer conjugate is optional, since after the insertion step, described below, the liposomes will include lipid-polymer-targeting ligand. Additional polymer chains added to the lipid mixture at the time of liposome formation and in the form of a lipid-polymer conjugate result in polymer chains extending from both the inner and outer surfaces of the liposomal lipid bilayers. Addition of a lipid-polymer conjugate at the time of liposome formation is typically achieved by including between 1-20 mole percent of the polymer-derivatized lipid with the remaining liposome forming components, e.g., vesicle-forming lipids. Exemplary methods of preparing polymer-derivatized lipids and of forming polymer-coated liposomes have been described in U.S. Pat. Nos. 5,013,556, 5,631,018 and 5,395,619, which are incorporated herein by reference. It will be appreciated that the hydrophilic polymer may be stably coupled to the lipid, or coupled through an unstable linkage, which allows the coated liposomes to shed the coating of polymer chains as they circulate in the bloodstream or in response to a stimulus.

The liposomes also include a therapeutic or diagnostic agent, and exemplary agents are provided below. The selected agent is incorporated into liposomes by standard methods, including (i) passive entrapment of a water-soluble compound by hydrating a lipid film with an aqueous solution of the agent, (ii) passive entrapment of a lipophilic compound by hydrating a lipid film containing the agent, and (iii) loading an ionizable drug against an inside/outside liposome pH gradient. Other methods, such as reverse-phase evaporation, are also suitable.

After liposome formation, the liposomes can be sized to obtain a population of liposomes having a substantially homogeneous size range, typically between about 0.01 to 0.5 microns, more preferably between 0.03-0.40 microns. One effective sizing method for REVs and MLVs involves extruding an aqueous suspension of the liposomes through a series of polycarbonate membranes having a selected uniform pore size in the range of 0.03 to 0.2 micron, typically 0.05, 0.08, 0.1, or 0.2 microns. The pore size of the membrane corresponds roughly to the largest sizes of liposomes produced by extrusion

through that membrane, particularly where the preparation is extruded two or more times through the same membrane. Homogenization methods are also useful for down-sizing liposomes to sizes of 100 nm or less (Martin, F. J., in SPECIALIZED DRUG DELIVERY SYSTEMS – MANUFACTURING AND PRODUCTION TECHNOLOGY, P. Tyle, Ed., Marcel Dekker, New York, pp. 267-316 (1990)).

After formation of the liposomes, a targeting ligand is incorporated to achieve a target-cell sensitized, therapeutic liposome. The targeting ligand is incorporated by incubating the pre-formed liposomes with the lipid-polymer-ligand conjugate, prepared as described above. The pre-formed liposomes and the conjugate are incubated under conditions effective to achieve insertion of the conjugate into the liposome bilayer. More specifically, the two components are incubated together under conditions which achieve insertion of the conjugate in such a way that the targeting ligand is oriented outwardly from the liposome surface, and therefore available for interaction with its cognate receptor. It will be appreciated that the conditions effective to achieve insertion of the targeting conjugate into the liposome are determined based on several variables, including, the desired rate of insertion, where a higher incubation temperature may achieve a faster rate of insertion, the temperature to which the ligand can be safely heated without affecting its activity, and to a lesser degree the phase transition temperature of the lipids and the lipid composition. It will also be appreciated that insertion can be varied by the presence of solvents, such as amphipathic solvents including polyethyleneglycol and ethanol, or detergents.

The targeting conjugate, in the form of a lipid-polymer-ligand conjugate, will typically form a solution of micelles when the conjugate is mixed with an aqueous solvent. The micellar solution of the conjugates is mixed with a suspension of pre-formed liposomes for insertion of the conjugate into the liposomal lipid bilayers. The invention includes, in another aspect, a plurality of targeting conjugates, such as a micellar solution of targeting conjugates, for use in preparing a targeted, therapeutic liposome composition. Each conjugate is composed of (i) a lipid having a polar head group and a hydrophobic tail, (ii) a hydrophilic polymer having a proximal end and a distal end, where the polymer is attached at its proximal end to the head group of the lipid, and (iii) a targeting ligand

attached to the distal end of the polymer.

The invention also contemplates a method of formulating a therapeutic liposome composition having sensitivity to a target cell. The method includes the steps of (i) providing a liposome formulation composed of pre-formed liposomes having an entrapped therapeutic agent; (ii) providing a targeting conjugate composed of (a) a lipid having a polar head group and a hydrophobic tail, (b) a hydrophilic polymer having a proximal end and a distal end, where the polymer is attached at its proximal end to the head group of the lipid, and (c) a piperidinoyl carboxylic acid compound as a targeting ligand attached to the distal end of the polymer; (iii) combining the liposome formulation and the targeting conjugate to form the therapeutic, target-cell sensitive liposome composition. In one embodiment, combining includes incubating under conditions effective to achieve insertion of the selected targeting conjugate into the liposomes of the selected liposome formulation.

3.E. Therapeutic Uses and Agents

The liposomes include a therapeutic or diagnostic agent in entrapped form. Entrapped is intended to include encapsulation of an agent in the aqueous core and aqueous spaces of liposomes as well as entrapment of an agent in the lipid bilayer(s) of the liposomes. Agents contemplated for use in the composition of the invention are widely varied, and examples of agents suitable for therapeutic and diagnostic applications are given below.

The targeting ligand included in the liposomes serve to direct the liposomes to a region, tissue, or cell bearing $\alpha_V\beta_3$, $\alpha_V\beta_5$, and/or $\alpha_V\beta_6$ integrin receptors. Targeting the liposomes to such a region achieves site specific delivery of the entrapped agent. Disease states having a strong $\alpha_V\beta_3$, $\alpha_V\beta_5$, and αIIbβ3 (also referred to as GPIIb/IIIa) integrin component in their etiologies include, but are not limited to, unstable angina, thromboembolic disorders or atherosclerosis (GPIIb/IIIa); thrombosis or restenosis (GPIIb/IIIa or $\alpha_V\beta_3$); restenosis (dual $\alpha_V\beta_3$/GPIIb/IIIa); rheumatoid arthritis, vascular disorders or osteoporosis ($\alpha_V\beta_3$); tumor angiogenesis, tumor metastasis, tumor growth,

multiple sclerosis, neurological disorders, asthma, vascular injury or diabetic retinopathy ($\alpha_V\beta_3$ or $\alpha_V\beta_5$); and, angiogenesis (dual $\alpha_V\beta_3/\alpha_V\beta_5$).

Additionally, $\alpha_V\beta_3$ ligands have been found to be useful in treating and/or inhibiting restenosis (i.e. recurrence of stenosis after corrective surgery on the heart valve), atherosclerosis, diabetic retinopathy, macular degeneration and angiogenesis (i.e. formation of new blood vessels) and inhibiting viral disease. Consequently the delivery of an appropriate therapeutic agent to would be expected to enhance this effect.

Moreover, the growth of tumors depends on an adequate blood supply, which in turn is dependent on the growth of new vessels into the tumor; thus, inhibition of angiogenesis can cause tumor regression in animal models (Harrison's Principles of Internal Medicine, **1991**, 12th ed.). Therefore, $\alpha_V\beta_3$ targeted liposome containing a therapeutic agent, which inhibit angiogenesis can be useful in the treatment of cancer by inhibiting tumor growth (Brooks et al., *Cell*, 79:1157-1164 (1994)). Evidence has also been presented suggesting that angiogenesis is a central factor in the initiation and persistence of arthritic disease and that the vascular integrin $\alpha_V\beta_3$ may be a preferred target in inflammatory arthritis. Therefore, $\alpha_V\beta_3$ targeted liposome that delivers an anti-angiogenesis or appropriate therapeutic to treat arthritis may represent a novel therapeutic approach to the treatment of arthritic disease, such as rheumatoid arthritis (C.M. Storgard, et al., *J. Clin. Invest.,* 103:47-54 (1999)).

Inhibition of the $\alpha_V\beta_5$ integrin receptor can also prevent neovascularization. A monoclonal antibody for $\alpha_V\beta_5$ has been shown to inhibit VEGF-induced angiogenesis in rabbit cornea and the chick chorioallantoic membrane model (M.C. Friedlander, et al., *Science*, 270:1500-1502 (1995)). Thus, $\alpha_V\beta_5$ targeted liposomes containing an appropriate therapeutic agent would be useful for treating and preventing macular degeneration, diabetic retinopathy, cancer, and metastatic tumor growth.

Inhibition of αv integrin receptors can also prevent angiogenesis and inflammation by acting as antagonists of other β subunits, such as $\alpha v\beta 6$ and $\alpha v\beta 8$ (Melpo

Christofidou-Solomidou, et al., *American Journal of Pathology,* 151:975-83 (1997); Xiao-Zhu Huang, et al., *Journal of Cell Biology,* 133:921-28 (1996)), again suggesting in disease states where angiogenesis or inflammation is to be treated that a αvβ6 targeted liposome containing an appropriate therapeutic agent would provide a novel therapy.

An antagonist to the αv integrin can act to inhibit or minimize adhesions that result from either wounding or surgical adhesions. Post-surgical adhesions result as an anomaly of the wound healing process. Cell adhesion and the migration of fibroblasts are major players in this process. Trauma caused by the wounding, a surgical procedure, normal tissue manipulation in surgery, or bleeding during a surgical procedure can act to disrupt the peritoneum and expose the underlying stroma leading to the release of inflammatory mediators and an increase in capillary permeability. Inflammatory cells are subsequently liberated and the formation of a fibrin clot ensues. Adhesions are formed and intensify as fibroblasts and inflammatory cells continue to infiltrate this extracellular matrix rich in fibrin. The extracellular matrix is composed of adhesive proteins which act as ligands for the αv integrin. The αv integrin targeted liposome containing an appropriate therapeutic agent can be administered before, during or after a surgical procedure.

Therapeutic agents include natural and synthetic compounds having the following therapeutic activities including but not limited to, steroids, immunosuppressants, antihistamines, non-steroidal anti-asthamtics, non-steroidal anti-inflammatory agents, cyclooxygenase-2 inhibitors, cytotoxic agents, gene therapy agents, radiotherapy agents, and imaging agents may be used in the targeted liposomes.

Examples of these compounds include (a) steroids such as beclomethasone, methylprednisolone, betamethasone, prednisone, dexamethasone, and hydrocortisone; (b) immunosuppressants such as FK-506 type immunosuppressants; (c) antihistamines (H1-histamine antagonists) such as bromopheniramine, chlorpheniramine, dexchlorpheniramine, triprolidine, clemastine, diphenhydramine, diphenylpyraline, tripelennamine, hydroxyzine, methdilazine, promethazine, trimeprazine, azatadine, cyproheptadine, antazoline, pheniramine pyrilamine, astemizole, terfenadine, loratadine,

cetirizine, fexofenadine, descarboethoxyloratadine, and the like; (d) non-steroidal anti-asthmatics such as b2-agonists (terbutaline, metaproterenol, fenoterol, isoetharine, albuterol, bitolterol, salmeterol and pirbuterol), theophylline, cromolyn sodium, atropine, ipratropium bromide, leukotriene antagonists (zafirlukast, montelukast, pranlukast, iralukast, pobilukast, SKB-106,203), leukotriene biosynthesis inhibitors (zileuton, BAY-1005); (e) non-steroidal antiinflammatory agents (NSAIDs) such as propionic acid derivatives (alminoprofen, benoxaprofen, bucloxic acid, carprofen, fenbufen, fenoprofen, fluprofen, flurbiprofen, ibuprofen, indoprofen, ketoprofen, miroprofen, naproxen, oxaprozin, pirprofen, pranoprofen, suprofen, tiaprofenic acid, and tioxaprofen), acetic acid derivatives (indomethacin, acemetacin, alclofenac, clidanac, diclofenac, fenclofenac, fenclozic acid, fentiazac, furofenac, ibufenac, isoxepac, oxpinac, sulindac, tiopinac, tolmetin, zidometacin, and zomepirac), fenamic acid derivatives (flufenamic acid, meclofenamic acid, mefenamic acid, niflumic acid and tolfenamic acid), biphenylcarboxylic acid derivatives (diflunisal and flufenisal), oxicams (isoxicam, piroxicam, sudoxicam and tenoxican), salicylates (acetyl salicylic acid, sulfasalazine) and the pyrazolones (apazone, bezpiperylon, feprazone, mofebutazone, oxyphenbutazone, phenylbutazone); (f) cyclooxygenase-2 (COX-2) inhibitors such as celecoxib, rofecoxib, and parecoxib; (g) cholesterol lowering agents such as HMG-CoA reductase inhibitors (lovastatin, simvastatin, pravastatin, fluvastatin, atorvastatin, and other statins), sequestrants (cholestyramine and colestipol), nicotinic acid, fenofibric acid derivatives (gemfibrozil, clofibrat, fenofibrate and benzafibrate), and probucol; (h) anti-diabetic agents such as insulin, sulfonylureas, biguanides (metformin), a-glucosidase inhibitors (acarbose) and glitazones (troglitazone, pioglitazone, englitazone, MCC-555, BRL49653 and the like); (1) agents that interfere with TNF such as antibodies to TNF (REMICADE®) or soluble TNF receptor (e.g. ENBREL®) ; (h) anticholinergic agents such as muscarinic antagonists (ipratropium nad tiatropium); (i) antimetabolites such as azathioprine and 6-mercaptopurine, and cytotoxic cancer chemotherapeutic agents.

The entrapped therapeutic agent is, in one embodiment, a cytotoxic drug. The drug can be an anthracycline antibiotic, including but not limited to doxorubicin, daunorubicin, epirubicin, and idarubicin, including salts and analogs thereof. The cytotoxic agent can also be a platinum compound, such as cisplatin, carboplatin,

ormaplatin, oxaliplatin, zeniplatin, enloplatin, lobaplatin, spiroplatin, ((-)-(R)-2-aminomethylpyrrolidine (1,1-cyclobutane dicarboxylato)platinum), (SP-4-3(R)-1,1-cyclobutane-dicarboxylato(2-)-(2-methyl-1,4-butanediamine-N ,N')platinum), nedaplatin and (bis-acetato-ammine-dichloro-cyclohexylamine-platinum(IV)). The cytotoxic agent can also be a topoisomerase 1 inhibitor, including but not limited to topotecan, irinotecan, (7-(4-methylpiperazino-methylene)-10,11-ethylenedioxy-20(S)-camptothecin), 7-(2-(N-isopropylamino)ethyl)-(20S)-camptothecin, 9-aminocamptothecin and 9-nitrocamptothecin. The cytotoxic agent can also be a vinca alkaloid such as vincristine, vinblastine, vinleurosine, vinrodisine, vinorelbine, and vindesine. The entrapped therapeutic agent can also be an angiogenesis inhibitor, such as angiostatin, endostatin and TNFα.

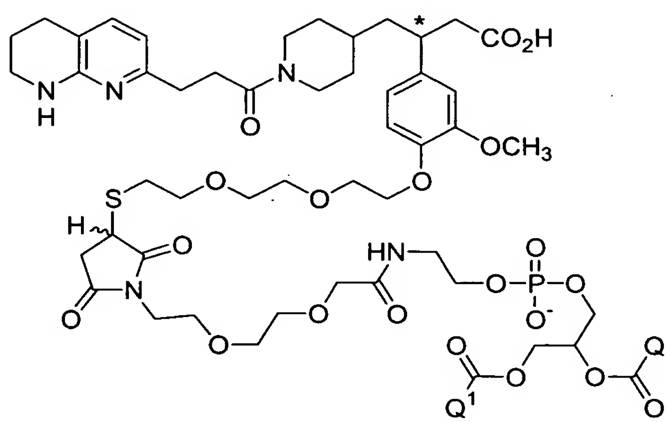
Nucleic acids are also contemplated for use as the therapeutic agent. DNA and RNA based nucleic acids, including fragments and analogues, can be used for treatment of various conditions, and coding sequences for specific genes of interest can be retrieved from DNA sequence databanks, such as GenBank or EMBL. For example, polynucleotides for treatment of viral, malignant and inflammatory diseases and conditions, such as, cystic fibrosis, adenosine deaminase deficiency and AIDS, have been described. Treatment of cancers by administration of tumor suppressor genes, such as APC, DPC4, NF-1, NF-2, MTS1, RB, p53, WT1, BRCA1, BRCA2 and VHL, are contemplated. Administration of the following nucleic acids for treatment of the indicated conditions are also contemplated: HLA-B7, tumors, colorectal carcinoma, melanoma; IL-2, cancers, especially breast cancer, lung cancer, and tumors; IL-4, cancer; TNF, cancer; IGF-1 antisense, brain tumors; IFN, neuroblastoma; GM-CSF, renal cell carcinoma; MDR-1, cancer, especially advanced cancer, breast and ovarian cancers; and HSV thymidine kinase, brain tumors, head and neck tumors, mesothelioma, ovarian cancer.

The polynucleotide can be an antisense DNA oligonucleotide composed of sequences complementary to its target, usually a messenger RNA (mRNA) or an mRNA precursor. The mRNA contains genetic information in the functional, or sense, orientation and binding of the antisense oligonucleotide inactivates the intended mRNA

and prevents its translation into protein. Such antisense molecules are determined based on biochemical experiments showing that proteins are translated from specific RNAs and once the sequence of the RNA is known, an antisense molecule that will bind to it through complementary Watson-Crick base pairs can be designed. Such antisense molecules typically contain between 10-30 base pairs, more preferably between 10-25, and most preferably between 15-20. The antisense oligonucleotide can be modified for improved resistance to nuclease hydrolysis, and such analogues include phosphorothioate, methylphosphonate, phosphodiester and p-ethoxy oligonucleotides (WO 97/07784). The entrapped agent can also be a ribozyme or catalytic RNA.

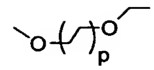
3.F. Exemplary Liposome Compositions

Liposomes were prepared in support of the invention as described in Example 40. The liposomes included a lipid-polymer-ligand conjugated having the structure of Formula 1(a):



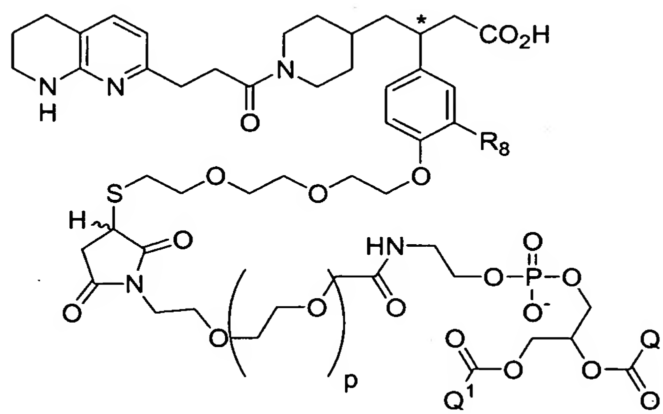
Formula (Ia)

It is recognized that there are two enantiomers of the targeting ligand or targeting conjugate and although the absolute configuration of the enantiomers is not known. It is recognized that one of the enantiomers is significantly more active that the other. The enantiomers can be resolved using conventional chiral separation techniques and the most active enantiomer will preferably be employed for the practice of the present invention.

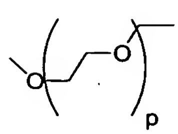
where Q and Q1 correspond to C17 of stearoic acid and the  moiety corresponds to poly(ethylene glycol) with a molecular weight of 3400 Daltons.

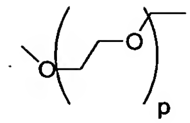
As described in Example 40, pre-formed liposomes were prepared from the lipids HSPC, cholesterol, and mPEG-DSPE. The therapeutic agent doxorubicin was loaded into the liposomes by remote loading against an ammonium ion gradient. The Formula (1a) targeting conjugate was inserted to the pre-formed liposomes by incubation of the conjugate at various concentrations with a fixed amount of liposomes. Three liposome formulations were prepared, differing only in the number of targeting ligands inserted into the outermost lipid bilayers of the pre-formed liposomes. As described in Example 40, liposomes having 18, 31, and 63 ligands per liposome were prepared.

Compounds having a structure represented by Formula (1b) are also suitable for use as liposomal targeting conjugates and for transfer via insertion into pre-formed liposomes:

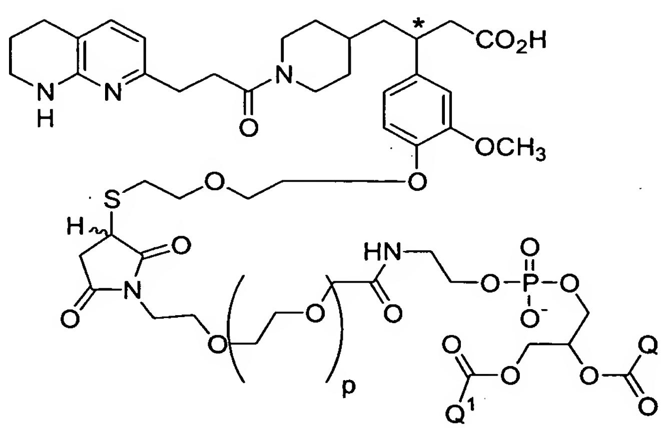


Formula (Ib)

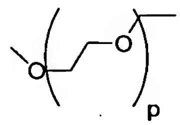
wherein R_8, the  moiety, Q, and Q^1 can be:

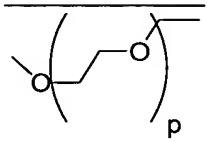
Targeting Conjugate No.	R_8		Q/ Q^1
TA-1	OCH_3	PEG 2000	C17 of stearoic acid
TA-2	OCH_3	PEG 5000	C17 of stearoic acid
TA-3	OCH_3	PEG 2000	C15 of palmitoic acid
TA-4	OCH_3	PEG 3400	C15 of palmitoic acid
TA-5	OCH_3	PEG 5000	C15 of palmitoic acid
TA-6	H	PEG 2000	C17 of stearoic acid
TA-7	H	PEG 3400	C17 of stearoic acid
TA-8	H	PEG 5000	C17 of stearoic acid

Compounds having a structure represented by Formula (1c) are also suitable for use as liposomal targeting conjugates and for transfer via insertion into pre-formed liposomes:

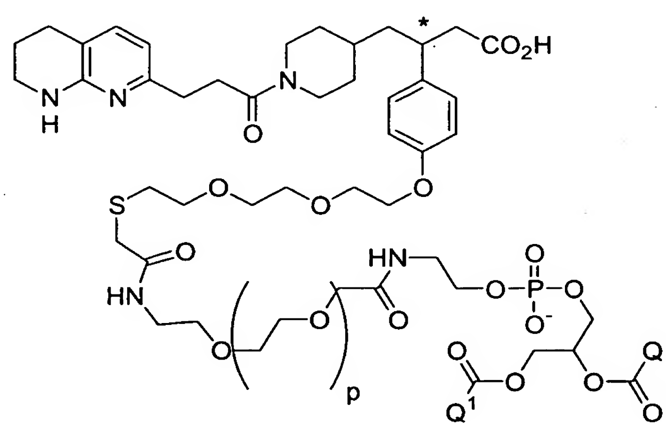


Formula (Ic)

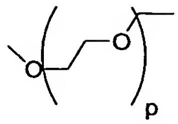
wherein the  moiety, Q, and Q[1] can be:

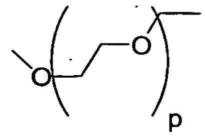
Targeting Conjugate No.		Q and Q[1]
TA-9	PEG 2000	C17 of stearoic acid
TA-10	PEG 5000	C17 of stearoic acid
TA-11	PEG 2000	C17 of oleoic acid
TA-12	PEG 3400	C17 of stearoic acid
TA-13	PEG 5000	C17 of oleoic acid

Compounds having a structure represented by Formula (1d) are also suitable for use as liposomal targeting conjugates and for transfer via insertion into pre-formed liposomes:

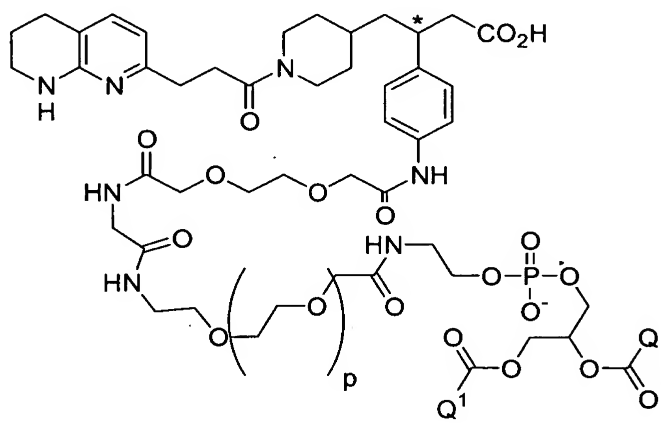


Formula (Id)

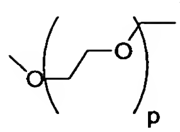
wherein the  moiety, Q, and Q^1 can be:

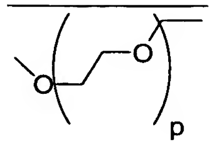
TARGETING AGENT		Q and Q^1
TA-14	PEG 3400	C17 of stearoic acid
TA-15	PEG 3400	C15 of palmitoic acid
TA-16	PEG 2000	C17 of stearoic acid

Compounds having a structure represented by Formula (1e) are also suitable for use as liposomal targeting conjugates and for transfer via insertion into pre-formed liposomes:

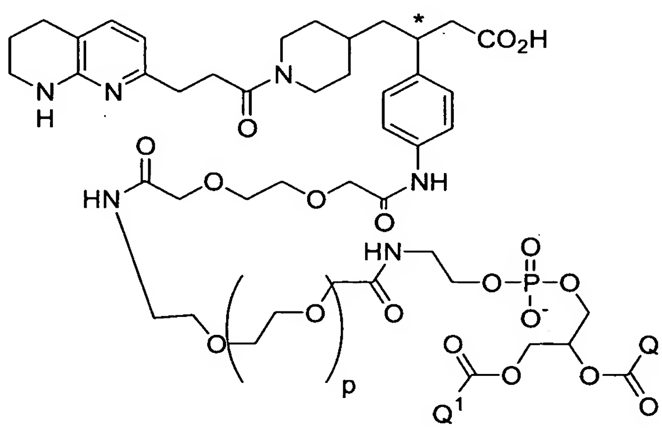


Formula (Ie)

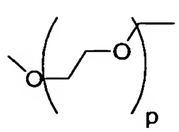
wherein the  moiety, Q, and Q^1 can be:

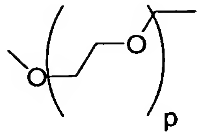
Targeting Conjugate No.		Q and Q^1
TA-17	PEG 5000	C17 of stearoic acid
TA-18	PEG 3400	C17 of stearoic acid
TA-19	PEG 2000	C17 of stearoic acid

Compounds having a structure represented by Formula (1f) are also suitable for use as liposomal targeting conjugates and for transfer via insertion into pre-formed liposomes:

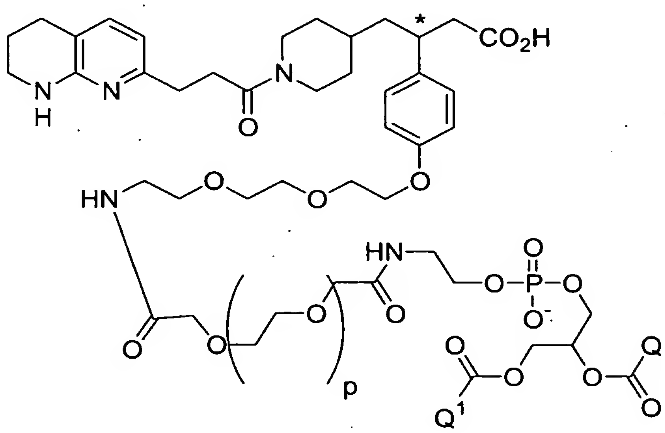


Formula (If)

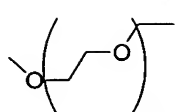
wherein the  moiety, Q, and Q^1 can be:

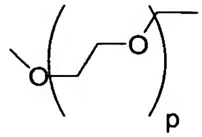
Targeting Conjugate No.		Q and Q[1]
TA-20	PEG 5000	C17 of stearoic acid
TA-21	PEG 3400	C17 of stearoic acid
TA-22	PEG 2000	C17 of stearoic acid

Compounds having a structure represented by Formula (1g) are also suitable for use as liposomal targeting conjugates and for transfer via insertion into pre-formed liposomes:



Formula (Ig)

wherein the  moiety, Q, and Q[1] can be:

Targeting Conjugate No.		Q and Q[1]
TA-23	PEG 5000	C17 of stearoic acid
TA-24	PEG 3400	C17 of stearoic acid
TA-25	PEG 2000	C17 of stearoic acid

Compounds having structures represented by Formulas (1a)-(1g) can be inserted into pre-formed liposomes by the method described in Example 40.

The invention also contemplates, in another aspect, a composition comprised of compound selected from compounds represented by Formula (1a)-(1g) and a solvent, to form a micellar solution of the compound. Such a micellar solution can be used during preparation of therapeutic, target-cell sensitized liposomes by the manufacturer, the clinician, the pharmacist, or the patient.

As described above, the therapeutic, target-cell sensitized liposomes can be administered to patients suffering from a disorder having an αvβ3, αvβ5, and/or αIIbβ3 (also referred to as GPIIb/IIIa) integrin component in its etiology. The targeting ligand, i.e., the piperidinoyl carboxylic acid compound, directs the drug-laden liposomes to cells expressing one or more of these integrin receptors. Biological Example 5 describes administration of liposomes, targeted with Cpd 39 (Example 39) and loaded with doxorubicin to mice.

Abbreviations used in the instant specification, particularly the Schemes and Examples, are as follows:

Boc	*tert*-butoxycarbonyl
BSA	Bovine Serum Albumen
Cod	Cyclooctadiene
d/hr/min/rt	day(s)/hour(s)/minute(s)/room temperature
DBC	2,6-Dichlorobenzoylchloride

DCM	Dichloromethane
DIEA	Diisopropylethylamine
DMA	Dimethylacetamide
DMAP	Dimethylaminopyridine
DMF	*N, N*-Dimethylformamide
DMSO	Dimethyl sulfoxide
EDC	*N*-ethyl-*N'*-dimethylaminopropylcarbodiimide hydrochloride
Et_2O	Diethyl ether
EtOAc	Ethyl acetate
EtOH	Ethanol
HATU	*O*-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium Hexafluorophosphate
HBTU	*O*-Benzotriazol-1-yl-*N,N,N',N'*- tetramethyluronium Hexafluorophosphate
HCl	Hydrochloric acid
HOBt	1-Hydroxybenzotriazole
HPLC	High Performance Liquid Chromatography
LDA	lithium diisopropylamide
LiHMDS	lithium hexamethyldisilylamide
Me	Methyl
MeOH	Methanol
MeCN	Acetonitrile
NaHMDS	sodium hexamethyldisilylamide
NaOH	Sodium hydroxide
ND	Not Determined
NMM	*N*-Methylmorpholine
PBS	Phosphate Buffer Solution
Ph	Phenyl
RP-HPLC	Reverse Phase High Performance Liquid Chromatography
rt	Room Temperature
SDS	Sodium dodecasulfate
TEA	Triethylamine
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
Thi	Thienyl
TMS	Tetramethylsilane
TFA	Trifluoroacetic acid
Tol	Toluene

General Synthetic Methods

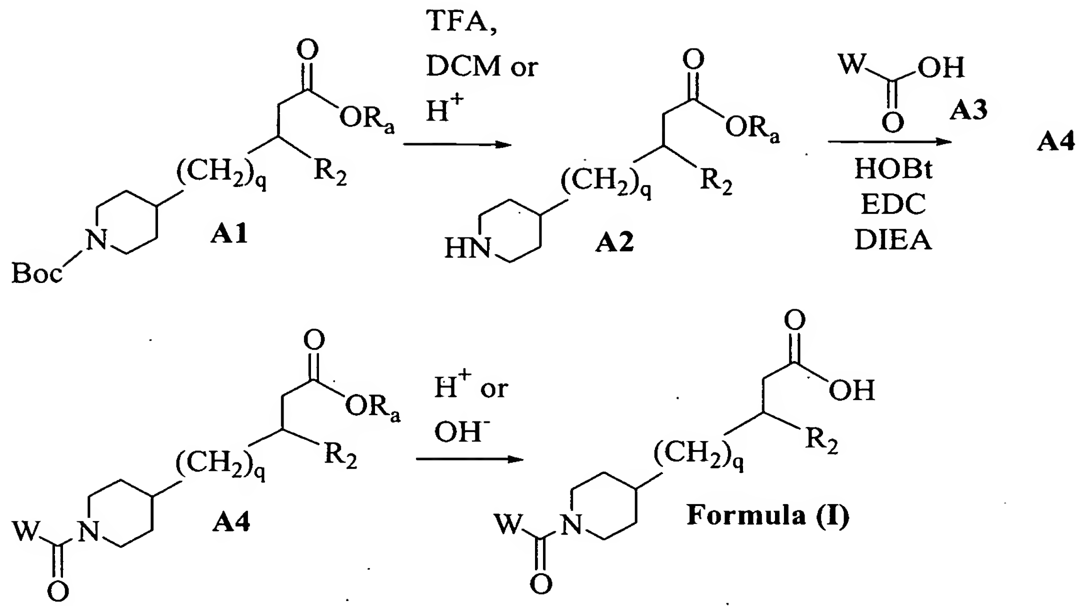
Representative compounds of the present invention can be synthesized in accordance

with the general synthetic methods described below and are illustrated more particularly in the schemes that follow. Since the schemes are illustrations whereby intermediate and target compounds of the present invention may be prepared, the invention should not be construed as being limited by the chemical reactions and conditions expressed. Additional representative compounds and stereoisomers, racemic mixtures, diastereomers and enantiomers thereof can be synthesized using the intermediates prepared in accordance with these schemes and other materials, compounds and reagents known to those skilled in the art. All such compounds, stereoisomers, racemic mixtures, diastereomers and enantiomers thereof are intended to be encompassed within the scope of the present invention. The preparation of the various starting materials used in the schemes is well within the skill of persons versed in the art.

Scheme A

Scheme A describes a method for preparing a target compound of Formula (I) (wherein R_1 and W are as previously defined within the scope of the invention. Removal of the Boc-protective group from a R_a substituted (wherein R_a is C_{1-4}alkyl) Compound **A1** was accomplished under acidic conditions (by using an acid such as an acidic mixture of TFA and DCM or an inorganic acid in an appropriate solvent such as dioxane) and resulted in formation of a piperidine Compound **A2**. Coupling of the piperidine Compound **A2** with a carboxylic acid Compound **A3** under standard coupling conditions (by using a mixture of coupling agents such as HOBt/EDC, HOBT/HBTU or isobutyl chloroformate in the presence of a suitable base such as NMM or DIEA) afforded the ester Compound **A4**. Hydrolysis of the ester Compound **A4** under acidic or basic conditions yielded a target compound Formula (I). The individual isomers of Formula (I) can be achieved through the chiral separation of intermediate **A1** - **A4**, and elaboration of the chiral intermediates to compounds of Formula (I).

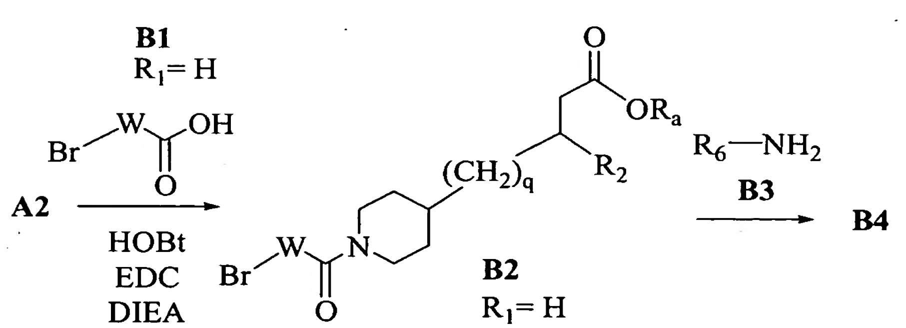
Scheme A

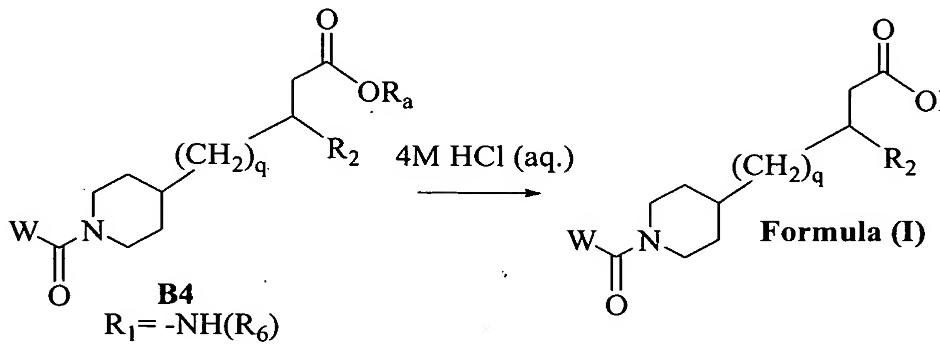


Scheme B

Scheme B describes an alternative method for preparing a target compound of Formula (I) (wherein R_1 is -NH(R_6) and W is -(CH_2)$_{0\text{-}4}$alkyl-). Condensation of a Compound **A2** with a Compound **B1** (wherein R_1 is H) possessing a suitable leaving group such as a halogen or a mesylate or tosylate under standard coupling conditions (by using a mixture of coupling agents such as HOBt/EDC, HOBT/HBTU or isobutyl chloroformate in the presence of a suitable base such as NMM or DIEA) resulted in the formation of Compound **B2**. Reaction of Compound **B2** with a substituted amine Compound **B3** in the presence of an appropriate base such as LiHMDS, NaHMDS or LDA resulted in the formation of Compound **B4**. Treatment of Compound **B4** with aqueous hydrochloric acid resulted in hydrolysis of the ester to yield a target compound of Formula (I).

Scheme B

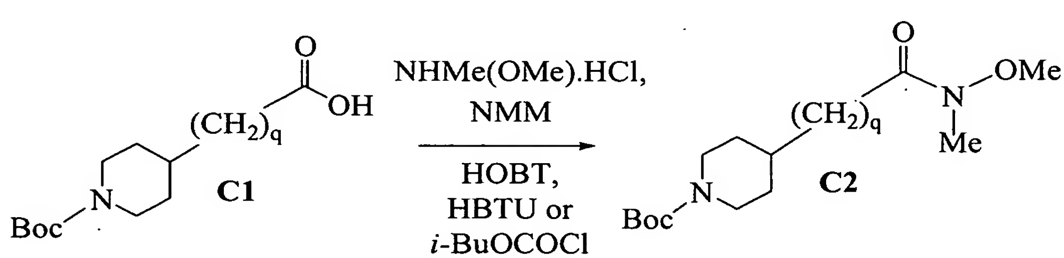


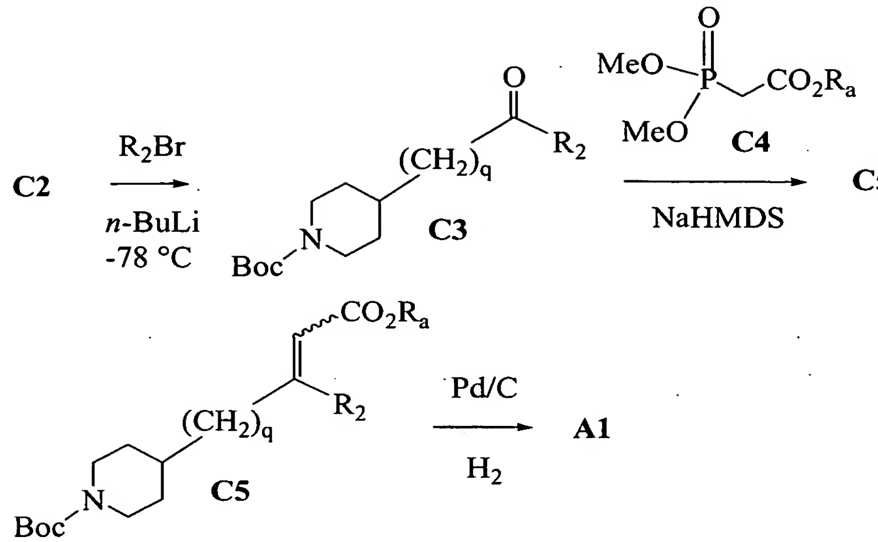


Scheme C

Scheme C describes an alternative method whereby a Compound **A1** may be prepared. Carboxylic acid Compound **C1** was transformed into an amide Compound **C2** using *N*-methyl-*O*-methylhydroxylamine in the presence of an appropriate activating agent such as HOBt, HBTU, HATU, isobutyl chloroformate or the like. Reaction of the amide Compound **C2** with an *in situ* prepared aryl lithium species, a Grignard reagent or the like resulted in the formation of a ketone Compound **C3**. The ketone Compound **C3** was converted to a mixture of *cis* and *trans* isomers of an α,β-unsaturated ester Compound **C5** upon reaction with an appropriately substituted phosphorane or phosphonate Compound **C4** in the presence of a base such as LiHMDS, NaHMDS, LDA or the like. Conversion of Compound **C5** to Compound **A1** was accomplished under hydrogenolysis conditions (wherein a hydrogen overpressure of from about 10 to about 50 psi was used) in the presence of an appropriate catalyst such as 5 or 10% palladium on carbon.

Scheme C

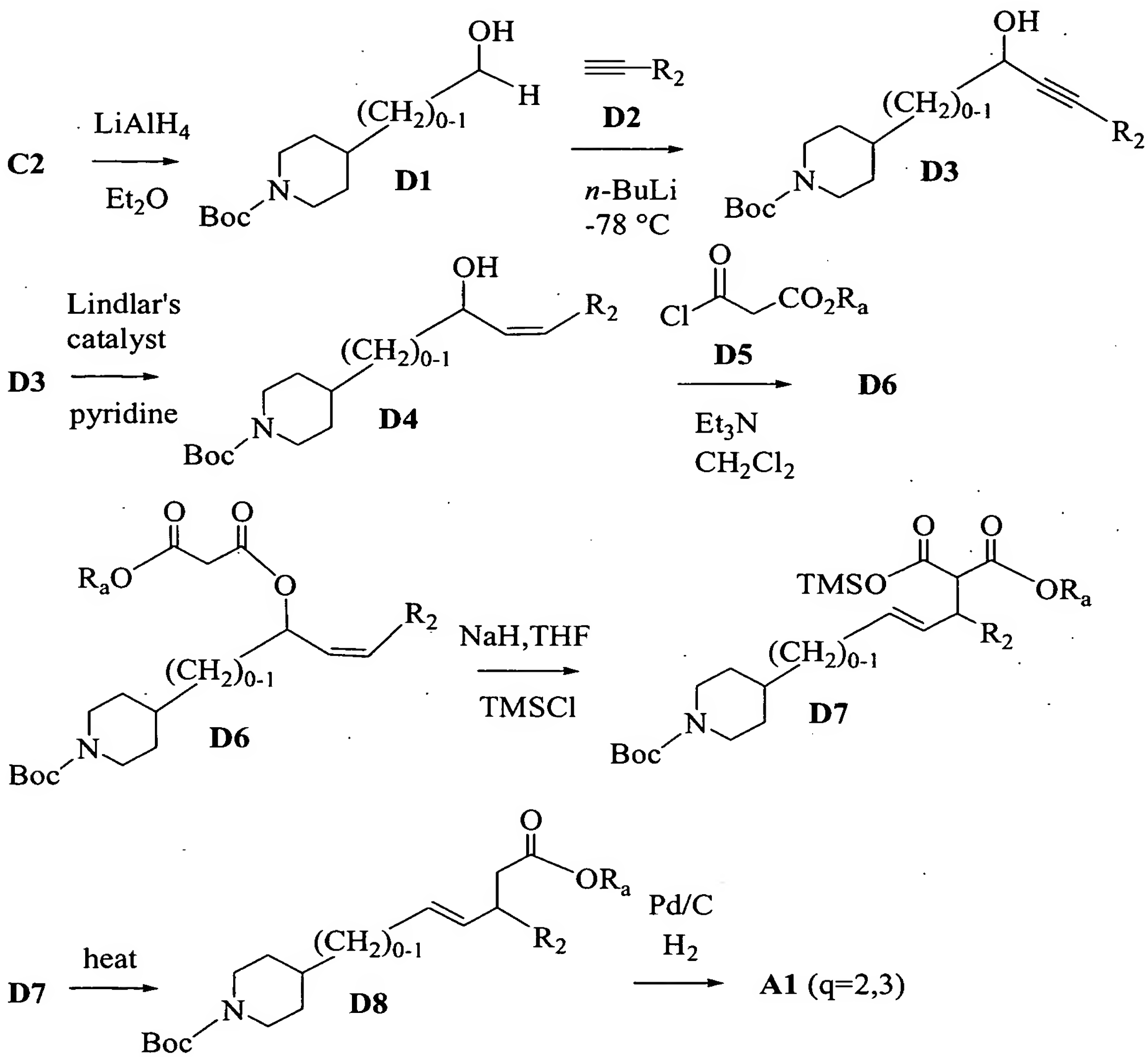




Scheme D

Scheme D describes an alternative method for the synthesis of a Compound **A1** in which $(CH_2)_q$ is $(CH_2)_{2\text{-}3}$. Reaction of an amide Compound **C2** with an appropriate reducing agent such as lithium aluminum hydride or the like resulted in the formation of an aldehyde Compound **D1**. Condensation of an *in situ* generated acetylide Compound **D2** with the aldehyde Compound **D1** at a low temperature resulted in formation of a propargylic alcohol Compound **D3**. The alkyne Compound **D3** was selectively reduced to a *cis*-olefin Compound **D4** under hydrogenolysis conditions using Lindlar's catalyst in pyridine. Condensation of the allylic alcohol Compound **D4** with an R_a substituted 3-chloro-3-oxopropionate Compound **D5** in the presence of a base such as TEA, DIEA or the like resulted in the formation of a mixed ester Compound **D6**. Treatment of Compound **D6** with chlorotrimethylsilane in the presence of a suitable base such as sodium hydride, potassium hydride, LDA or the like gave rise to an intermediate silyl ketene acetal which rearranged upon heating in a suitable solvent such as THF or Et_2O to a mixed ester Compound **D7**. Decarboxylation of the ester Compound **D7** to form Compound **D8** was accomplished upon heating Compound **D7** under vacuum. Reduction of the double bond in Compound **D8** was accomplished under standard hydrogenation conditions, applying a hydrogen overpressure (of from about 10 to about 50 psi) in the presence of an appropriate catalyst such as 5 or 10% palladium on carbon resulted in formation of a target compound Compound **A1** in which $(CH_2)_q$ is $(CH_2)_{2\text{-}3}$.

Scheme D

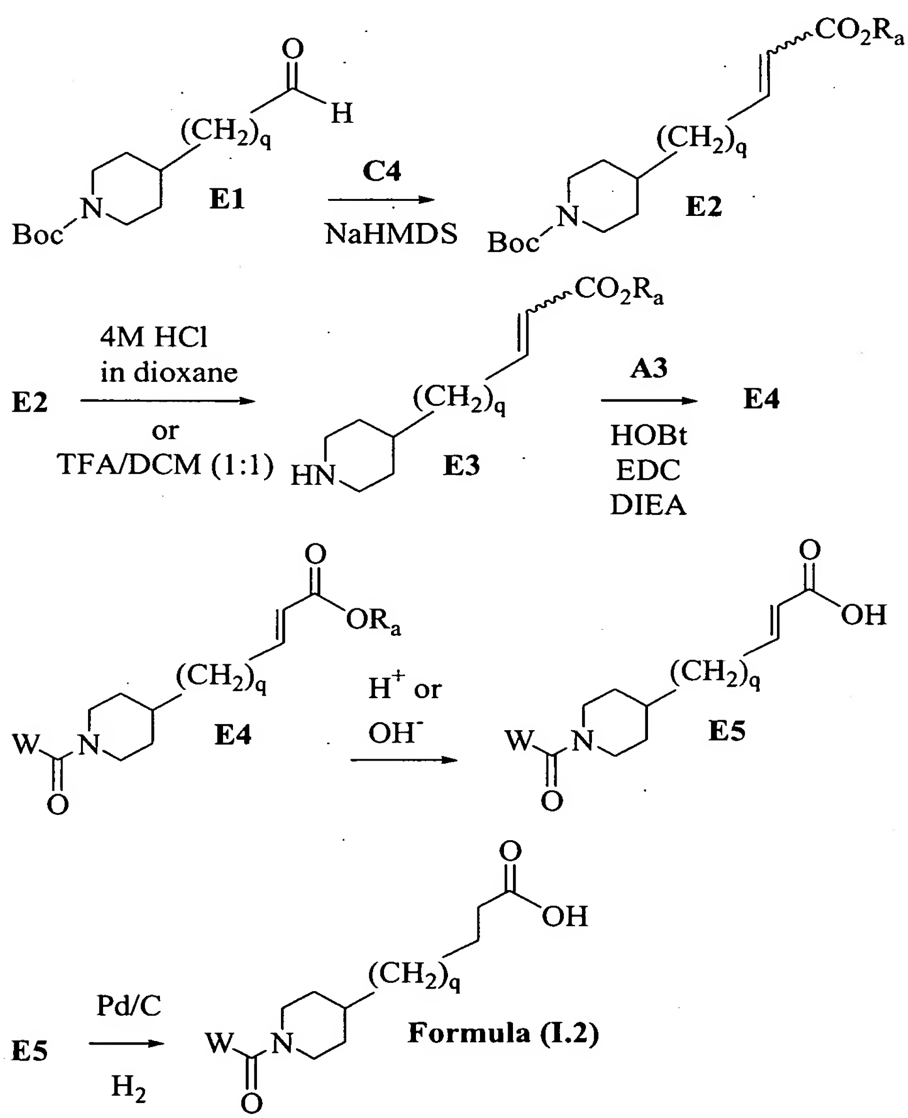


Scheme E

Scheme E describes an alternative method for the synthesis of a target compound of Formula (I.2) (wherein R_2 for a compound of Formula (I) is hydrogen, R_1 and W are as previously defined. Condensation of an aldehyde Compound **E1** using an appropriate carbalkoxymethylene triphenylphosphorane (Wittig reaction) or a trialkyl phosphonoacetate (Horner-Emmons reaction) resulted in the formation of an α,β-unsaturated ester Compound **E2**. Treatment of Compound **E2** under acidic conditions (using an acid such as a 1:1 mixture of TFA in DCM, 4N HCl in dioxane or the like) resulted in the removal of the Boc-protective group, resulting in formation of a substituted piperidine Compound **E3**. Coupling of the piperidine Compound **E3** with a

carboxylic acid Compound **A3** under standard coupling conditions (using a mixture of coupling agents such as HOBt/EDC, HOBT/HBTU or isobutyl chloroformate in the presence of a suitable base such as NMM or DIEA) resulted in an ester Compound **E4**. Hydrolysis of the ester Compound **E4** under acidic or basic conditions yielded an α,β-unsaturated acid Compound **E5**. Reduction of the double bond in Compound **E5** was accomplished under standard hydrogenation conditions, applying hydrogen overpressure (of from about 10 to about 50 psi) in the presence of an appropriate catalyst such as 5 or 10% palladium on carbon and resulted in the formation of a target compound of Formula (I.2).

Scheme E



Scheme F

Scheme F describes an alternative method whereby a target Compound **A1** may be prepared. A racemic E/Z-mixture of an α,β-unsaturated ester Compound **E2** was reacted with an R_2 substituted boronic acid Compound **F1** in the presence of an appropriate transition metal catalyst such as Rhodium or Indium to yield a target Compound **A1**.

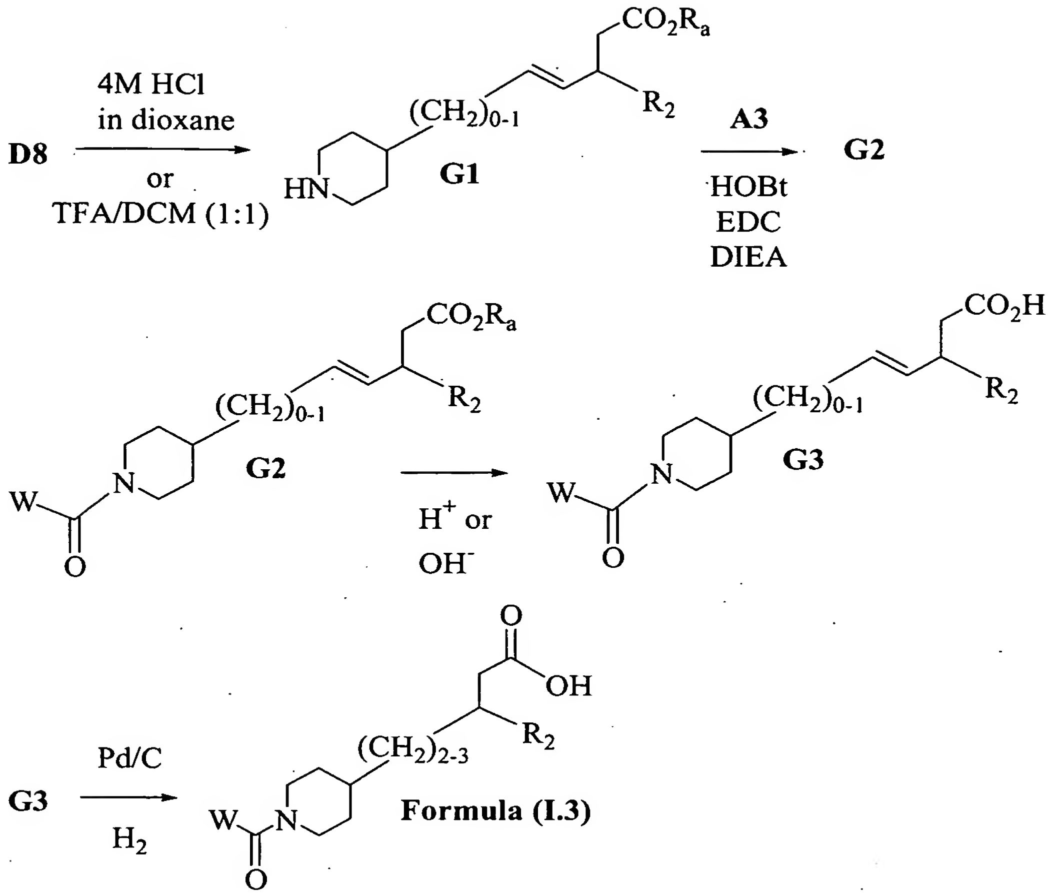
Scheme F

$$\mathbf{E2} \xrightarrow[\text{Rh(I) cat.}]{\substack{R_2\text{—}B(OH)_2 \\ \mathbf{F1}}} \mathbf{A1}$$

Scheme G

Scheme G describes an alternative method for the synthesis of a target compound of Formula (I.3) (wherein $(CH_2)_q$ for a compound of Formula (I) is $-(CH_2)_{2\text{-}3}-$, R_1 is as previously defined and W is $-(CH_2)_{0\text{-}4}$alkyl-). The Boc-protecting group on Compound **D8** was removed under acidic conditions (using an acid such as a 1:1 mixture of TFA in DCM, 4N HCl in dioxane or the like) to yield a substituted piperidine Compound **G1**. Coupling of the piperidine Compound **G1** with a carboxylic acid Compound **A3** under standard coupling conditions (using a mixture of coupling agents such as HOBt/EDC, HOBT/HBTU or isobutyl chloroformate in the presence of a suitable base such as NMM or DIEA) led to formation of an ester Compound **G2**. The ester Compound **G2** was be converted to Compound **G3** upon exposure to strong acidic or basic aqueous conditions (in the presence of a strong acid or base such as concentrated HCl or NaOH). The double bond in Compound **G3** was reduced using standard hydrogenation conditions, applying hydrogen overpressure (of from about 10 to about 50 psi) in the presence of an appropriate catalyst such as 5 or 10% palladium on carbon and resulted in the formation of a target compound of Formula (I.3).

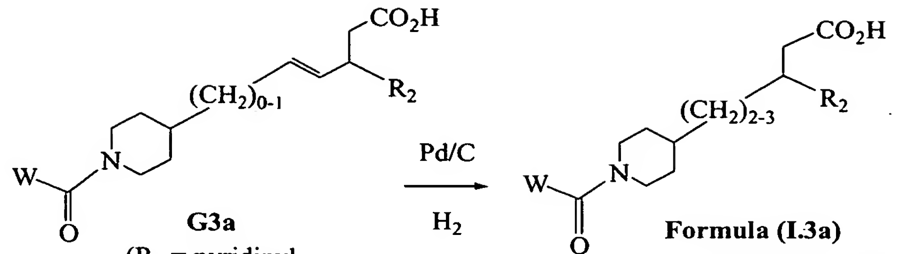
Scheme G



Scheme H

Scheme H describes a method for the synthesis of a target compound of Formula (I.3a) (wherein R_1 for a compound of Formula (I.3) is -NH(R_5), W is -$(CH_2)_{0-4}$alkyl- and an R_5 heteroaryl subtituent is reduced to a partially unsaturated heterocyclyl substituent) by reduction of the double bond in a Compound **G3a** (wherein R_1 in a Compound **G3** is -NH(R_5)) using standard hydrogenation conditions, applying hydrogen overpressure (of from about 10 to about 50 psi) in the presence of an appropriate catalyst such as 5 or 10% palladium on carbon, accompanied by standard reduction of R_5 to yield a target compound of Formula (I.3a).

Scheme H



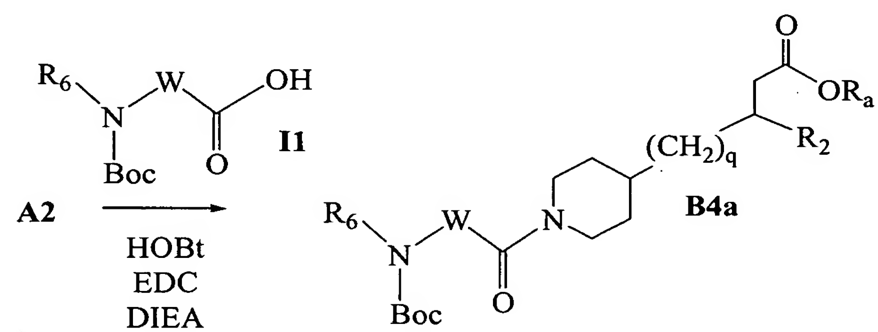
G3a (R_6 = pyridinyl, pyrimidinyl; R_1= -NH(R_5))

Formula (I.3a) (R_6 = tetrahydropyridinyl, tetrahydropyrimidinyl)

Scheme I

Scheme I describes an alternative method for the synthesis of a target Compound **B4a** (wherein $(CH_2)_q$ for the Compound **B4** is not limited to $-(CH_2)_{2\text{-}3}-$, R_6 is as previously defined, R_1 is H, and W is $-(CH_2)_{0\text{-}4}$alkyl-). Condensation of a Compound **A2** under standard coupling conditions (using a mixture of coupling agents such as HOBt/EDC, HOBT/HBTU or isobutyl chloroformate in the presence of a suitable base such as NMM or DIEA) with a protected amino acid Compound **I1** resulted in the formation of a target Compound **B4a**.

Scheme I

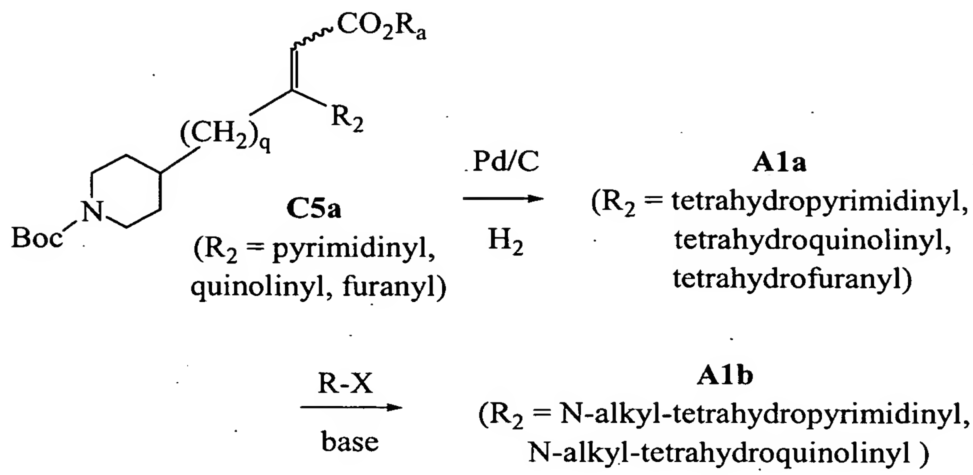


Scheme J

Scheme J describes a method for the synthesis of a target Compound **A1a** (wherein R_2 in a Compound **A1** is a heteroaryl subtituent that has been reduced to a partially or fully unsaturated heterocyclyl substituent). The double bond in Compound **C5a** (wherein R_2 in a Compound **C5** is a unsaturated heteroaryl subtituent) was reduced under standard hydrogenation conditions, applying hydrogen overpressure (of from about 10 to about 50 psi) in the presence of an appropriate catalyst such as 5 or 10% palladium on carbon, accompanied by standard reduction of R_2 to yield a target Compound **A1a**. Compound **A1a** can be separated into its individual optical isomers by chiral chromatography at

this stage. In addition, Compound **A1a** can be alkylated on the R_2 heteroatom using the appropriate alkylating agent such as iodomethane and the appropriate base such as 2,6-di-tert-butylpyridine to yield **A1b**.

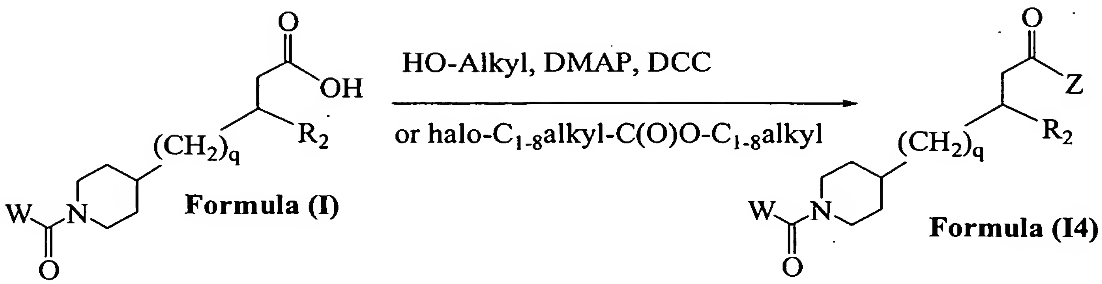
Scheme J



Scheme K

Scheme K describes a method for preparing a target compound of Formula **I4**. Treatment of a compound of Formula **I** with an appropriate alcohol in the presence of a coupling agent such as1,3-dicyclohexylcarbodiimide and an activating agent such as dimethylaminopyridine or the like resulted in the formation of target compound of Formula (**I4**). Alternatively, a compound of Formula **I** may be treated with an alkyl halide in the presence of a suitable base such as NMM or DIEA to yield a target compound of Formula **I4**.

Scheme K

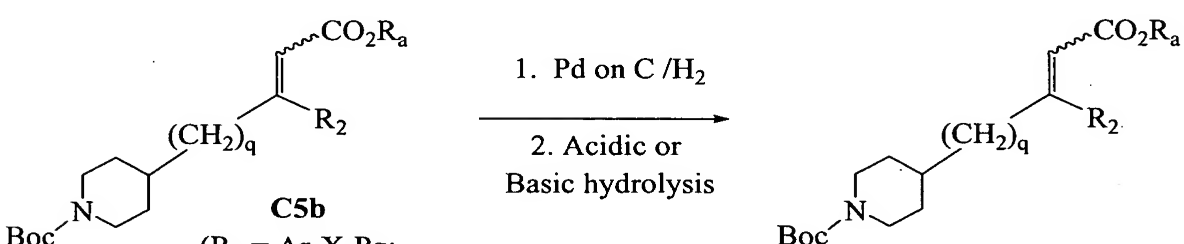


(Z = O-Alkyl,
-O-C_{1-8}alkyl-C(O)O-C_{1-8}alkyl)

Scheme L

Scheme L describes a method for the synthesis of a target compound of Formula **A1b** (wherein R_2 in a Compound **A1b** is a hydroxyaryl, aminoaryl, or thiophenyl substituent that has been deprotected). The double bond in Compound **C5b** (wherein R_2 in a Compound **C5** is an *O*-protected hydroxyaryl, *N*-protected anilino, or *S*-protected thioaryl substituent) was reduced under standard hydrogenation conditions, applying hydrogen overpressure (of from about 10 to about 50 psi) in the presence of an appropriate catalyst such as 5% or 10% palladium on carbon, accompanied by removal of the protective group to yield hydroxyaryl or anilino compound **A1b**. Alternatively, the protective group can be removed via basic or acidic hydrolysis in a subsequent step.

Scheme L



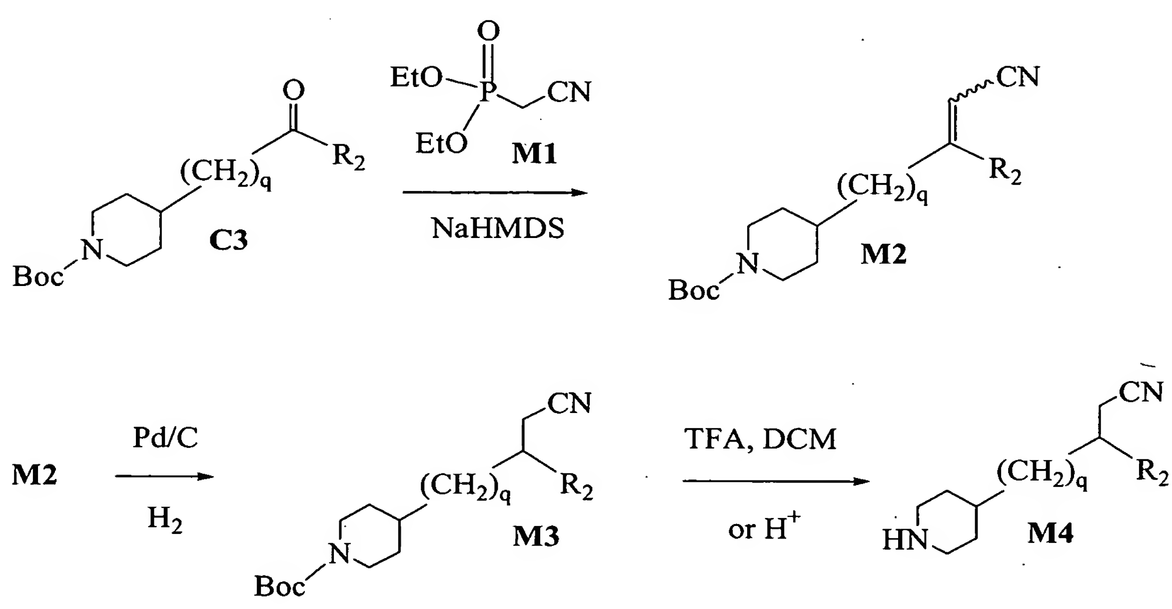
C5b
(R_2 = Ar-X-Pg;
X = NH, N-alkyl, O, S
Pg = protective group)

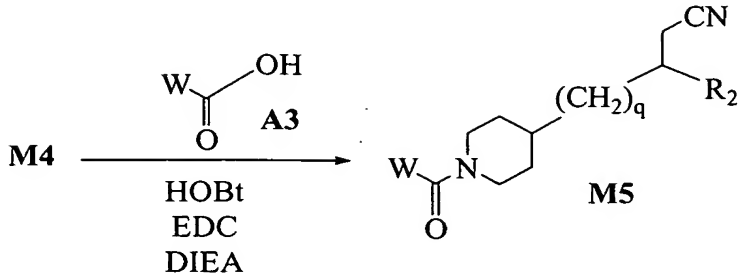
A1b
(R_2 = Ar-XH;
X = NH, N-alkyl, O, S)

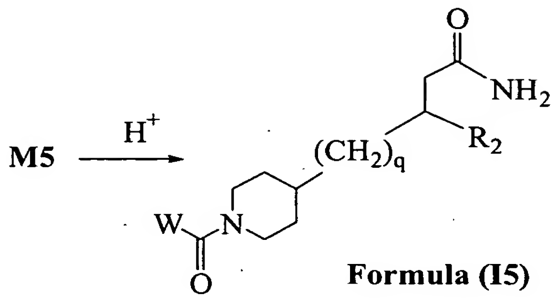
Scheme M

Scheme M describes a method for preparing a target compound of Formula (I5) (wherein R1 and W are as previously defined). The ketone Compound **C3** was

converted to a mixture of *cis* and *trans* isomers of an α,β-unsaturated nitriles Compound **M2** upon reaction with an appropriately substituted phosphorane or phosphonate Compound **M1** in the presence of a base such as LiHMDS, NaHMDS, LDA or the like. Conversion of Compound **M2** to Compound **M3** was accomplished under hydrogenolysis conditions (wherein a hydrogen overpressure of about 5 psi was used) in the presence of an appropriate catalyst such as 5 or 10% palladium on carbon. Removal of the Boc-protective group from Compound **M3** was accomplished under acidic conditions (by using an acid such as an acidic mixture of TFA and DCM or an inorganic acid in an appropriate solvent such as dioxane) and resulted in formation of a piperidine Compound **M4**. Coupling of the piperidine Compound **M4** with a carboxylic acid Compound **A3** under standard coupling conditions (by using a mixture of coupling agents such as HOBt/EDC, HOBT/HBTU or isobutyl chloroformate in the presence of a suitable base such as NMM or DIEA) afforded the nitrile Compound **M5**. Hydrolysis of the nitrile Compound **M5** under acidic conditions yielded a target compound of Formula (I5).





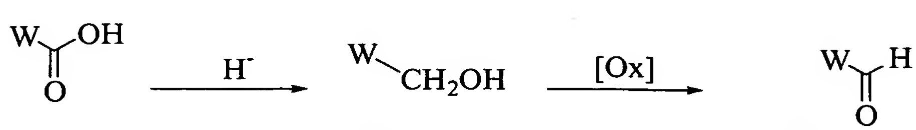


Formula (I5)

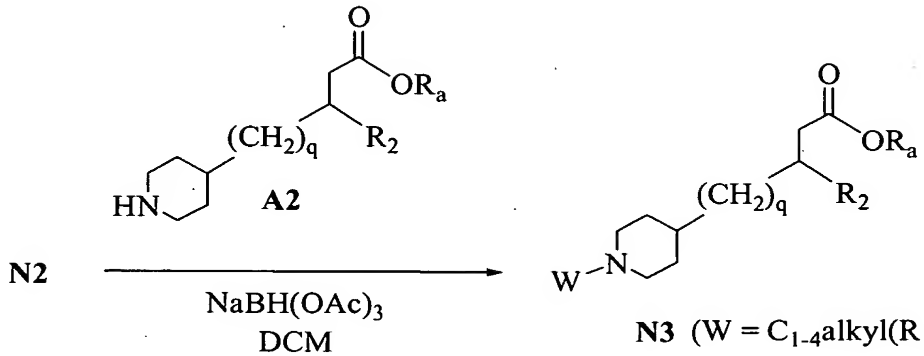
Scheme N

Scheme N describes a method for the synthesis of a target compound of Formula (II) (wherein W is defined as $C_{1\text{-}4}$alkyl(R_1)). Carboxylic acid Compound **A3** was transformed into alcohol Compound **N1** using an appropriate reducing agent such as lithium aluminum hydride or the like. Alchol Compound **N1** was transformed into aldehyde Compound **N2** using an appropriate oxidizing agent such as pyridinium chlorochromate or the like. Coupling of the aldehyde Compound **N2** with a piperidine Compound **A2** under standard reductive amination conditions using a reducing agent such as sodium triacetoxyborohydride or the like afforded the ester Compound **N3**. Hydrolysis of the ester Compound **N3** under acidic or basic conditions yielded a target compound Formula **(II)**.

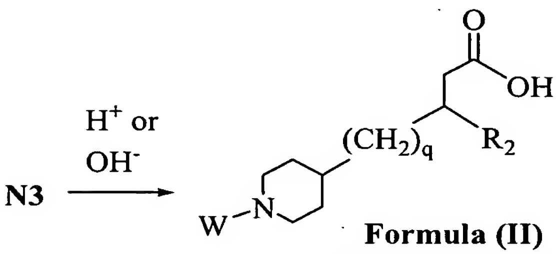
Scheme N



A3 (W = $C_{0\text{-}3}$alkyl(R_1)) **N1** **N2**



N3 (W = $C_{1\text{-}4}$alkyl(R_1))



Formula (II)
(W = $C_{1\text{-}4}$alkyl(R_1))

<u>Targeting Compounds</u>

The following schemes describe general synthetic methods whereby intermediate and target compounds of the present invention may be prepared. Additional representative compounds and stereoisomers, racemic mixtures, diasteromers and enantiomers thereof can be synthesized using the intermediates prepared in accordance to the general schemes and other materials, compounds and reagents known to those skilled in the art. All such compounds, stereoisomers, racemic mixtures, diasteromers and enantiomers thereof are intended to be encompassed within the scope of the present invention.

Those skilled in the art will recognize that the construction of compounds of the present invention may require manipulation of the reaction sequences presented herein so as to accommodate sensitive or reactive functional groups. Likewise, during any of the processes for preparation of the compounds described herein, it may be necessary and/or desirable to protect sensitive or reactive groups on any of the molecules concerned. This may be achieved by means of conventional protecting groups, such as those described in <u>Protective Groups in Organic Chemistry</u>, ed. J.F.W. McOmie, Plenum Press, 1973; and T.W. Greene & P.G.M. Wuts, <u>Protective Groups in Organic</u>

Synthesis, John Wiley & Sons, 1991. The protecting groups may be removed at a convenient subsequent stage using methods known in the art.

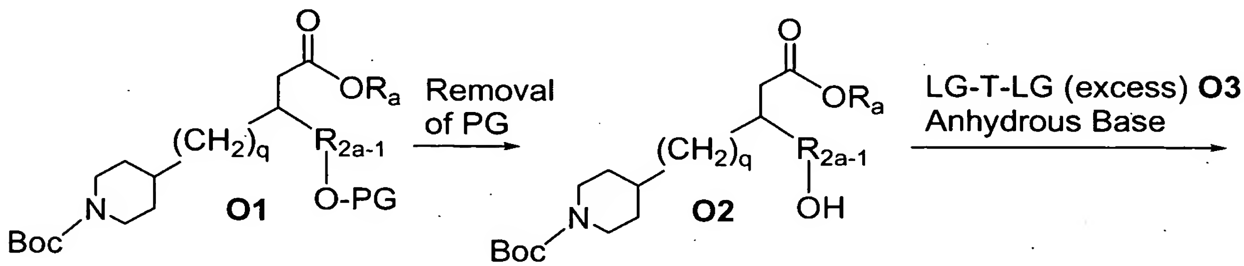
Scheme O

Scheme O describes a general method for the synthesis of compounds of the present invention. Compound **O1** is a compound wherein R_{2a} is a reactive form of R_2, meaning that it is equipped with a reactive functional group such as hydroxy or the like. Similarly, T as used herein is an activated precursor to R_{11} or R_{12} which possesses reactive functional groups at one or both of its ends. As demonstrated in Scheme O, the hydroxy functional group of Compound **O2** may be reacted with Compound **O3**, wherein LG is a leaving group such as chloride, bromide, iodide, or a sulfonate ester such as methane sulfonate, para-toluene sulfonate, or benzene sulfonate. Such compounds are commercially available or may be prepared using reagents and methods known to those skilled in the art. Alkylation of Compound **O2** under anhydrous basic conditions provides Compound **O4** which may then be converted to azide Compound **O5** via displacement of the leaving group (LG) by azide anion in a polar aprotic solvent. Compound **O5** may be deprotected under suitable acidic conditions to afford a free amine Compound **O6**. Subsequent acylation with Compound **O7** (wherein W_a is an activated precursor to W of the present invention) using previously described chemistry yields Compound **O8**. The azide functionality of Compound **O8** may be reduced to its corresponding primary amine using catalytic hydrogenation in an alcoholic solvent in the presence of a palladium catalyst and under a hydrogen pressure ranging from atmospheric pressure to 65 psi. Saponification of the ester under basic or acidic conditions, or using other chemistry for the deprotection of esters known to those skilled in the art, affords Compound **O9**.

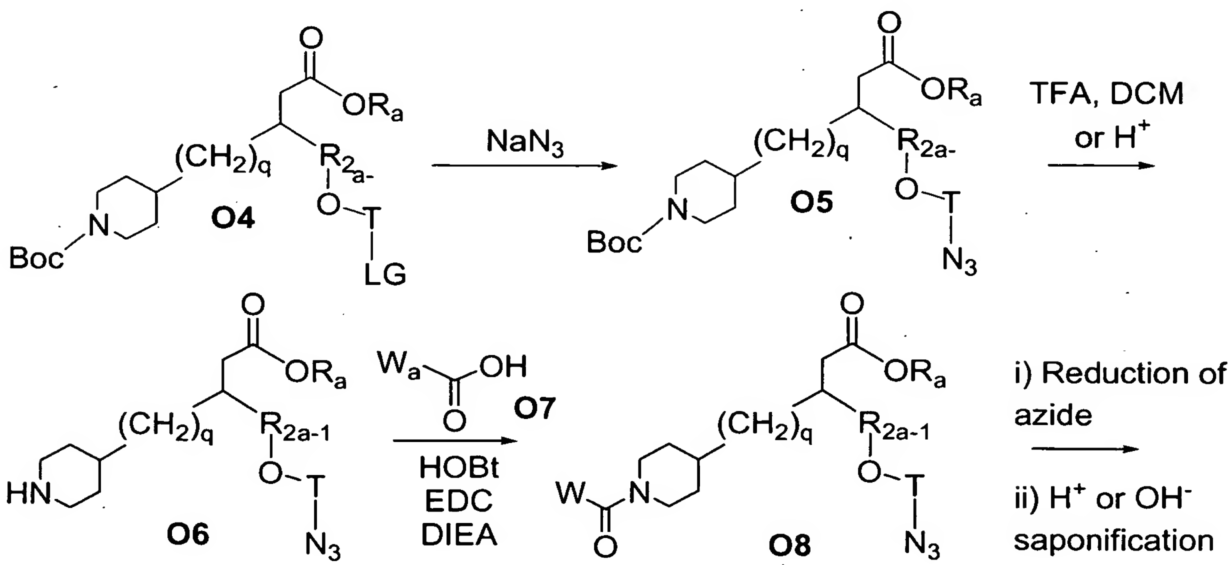
Compound **O9** may be reacted with a variety of activated precursors of R_{13}, such as Compound **O10**, to provide compounds of Formula (I). Activated precursors of R_{13} are either commercially available from suppliers (Avanti Polar Lipids, Inc., Alabaster AL; Nektar Therapeutics AL, Huntsville AL) or may be synthesized (Zalipsky, S. et al, *J. Control Release*, **1996**, 39, 153-161).

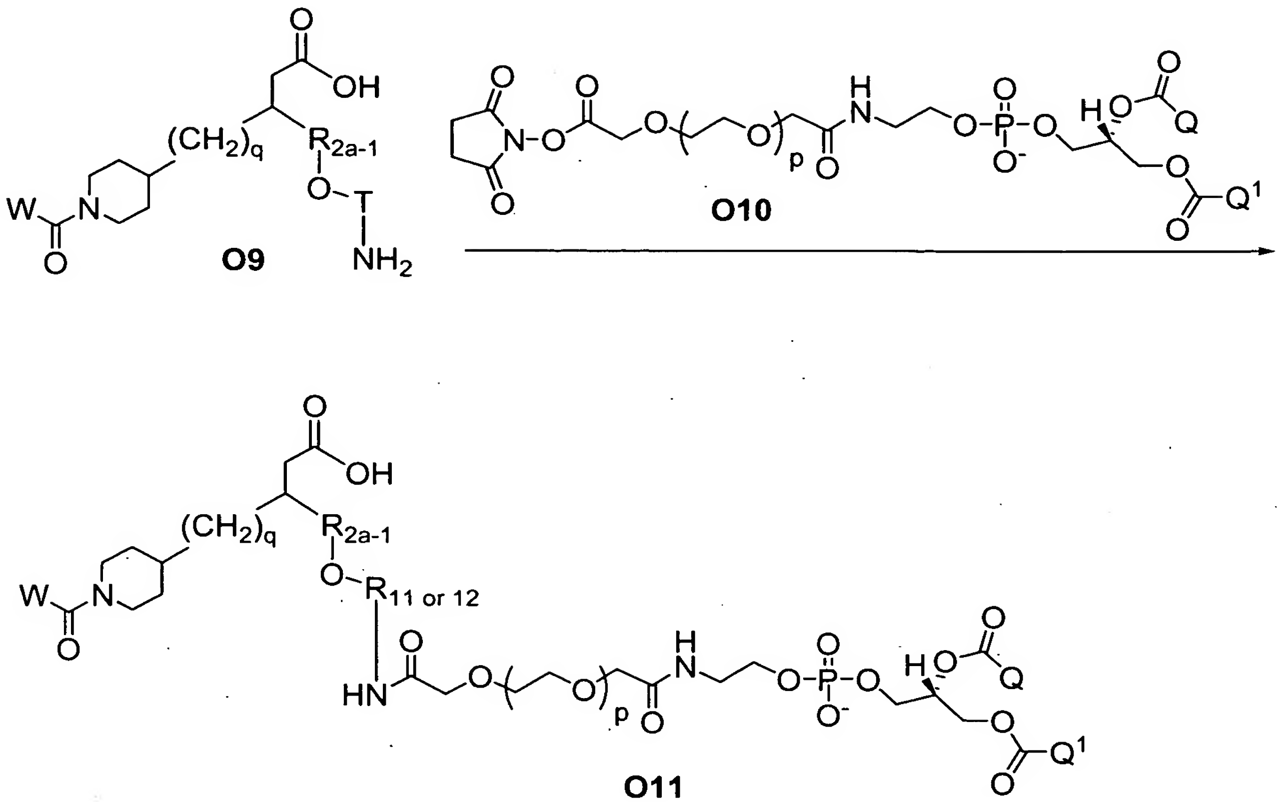
More specifically, Scheme O shows the acylation of the primary amine of **O9** with a hydroxyimide-activated ester, Compound **O10**, to give amide Compound **O11**. An amide linkage may also be accomplished using standard coupling reactions with appropriately activated R_{13} precursors. Those skilled in the art will recognize that intermediate Compound **O9** may be acylated with a variety of other R_{13} precursors activated with functional groups such as acid chlorides, formyl chlorides, anhydrides, α-halo-carbonyls, α/β-unsaturated carbonyls, isocyanates, and the like.

Scheme O



R_{2a-1} = R_{2a} precursor
PG = Protecting Group
LG-T-LG = precursor to $R_{11\ \mathrm{or}\ 12}$, each end terminating with a reactive LG
LG = Leaving Group

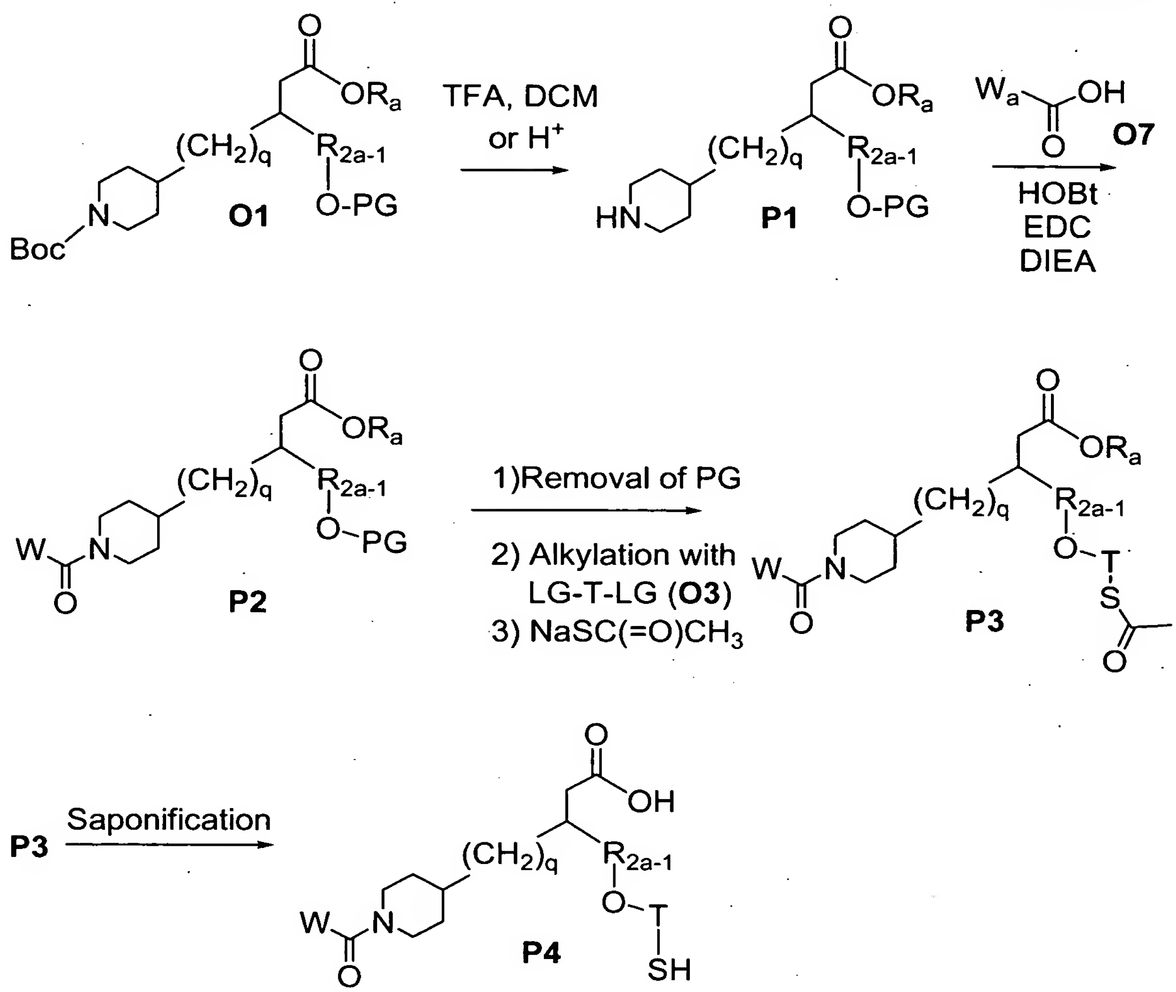




Scheme P

Compounds of the present invention may join R_{11} or R_{12} to R_{13} via a sulfur ether linkage. One method for the preparation of this class of compounds is shown in Scheme P which is a modification of Scheme O. The first step of Scheme P involves the deprotection of Compound **O1** to provide Compound **P1**, with subsequent coupling of the free amine with Compound **O7** to give Compound **P2**. Upon removal of the protecting group, Compound **P2** may be alkylated with Compound **O3** as described herein, followed by treatment with the sodium or potassium salt of thioacetic acid in an alcoholic or polar aprotic solvent (DMF or DMSO) to yield Compound **P3**. Saponification of the esters of Compound **P3** gives the free thiol, Compound **P4**.

<u>**Scheme P**</u>



Those skilled in the art will recognize that the thiol of Compound **P4** may be reacted with a number of activated precursors of R_{13} to yield compounds of the present invention. Examples of functional groups on the R_{13} terminus that would be reactive with a thiol are maleimido substituents, α-halo-carbonyls, α/β-unsaturated carbonyls, disulfides, and the like.

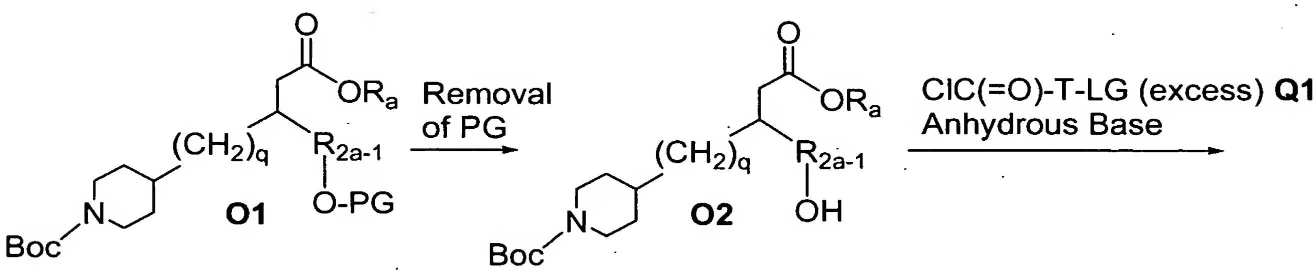
<u>Scheme Q</u>

Scheme Q shows a means for preparing of compounds of the present invention wherein R_{2a} is joined to R_{11} or R_{12} precursor, T, via an ester linkage. The hydroxy functionality of Compound **O2** may be reacted with a precursor of R_{11} or R_{12} activated with an acyl functional group such as an acid chloride, activated ester, or the like, to

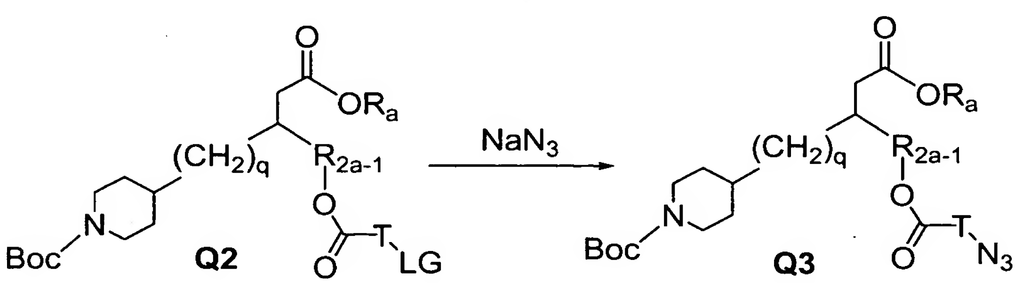
give Compound **Q2**, which may then be converted to azide Compound **Q3** using chemistry discussed above. Compound **Q3** may be further elaborated using chemistry described herein to prepare a compound of Formula (I).

Accordingly, Compound **Q2** may be treated with the sodium or potassium salt of thioacetic acid and further elaborated using conventional reagents and methods known to those skilled to provide a terminal thiol. The resulting thiol may be reacted with an activated precursor of R_{13} as discussed herein to give compounds of the present invention.

Scheme Q



R_{2a-1} = R_2 precursor
PG = Protecting Group
ClC(=O)-T-LG = precursor to $R_{11\ \text{or}\ 12}$ where one end is activated and the other terminates with a reactive LG
LG = Leaving Group

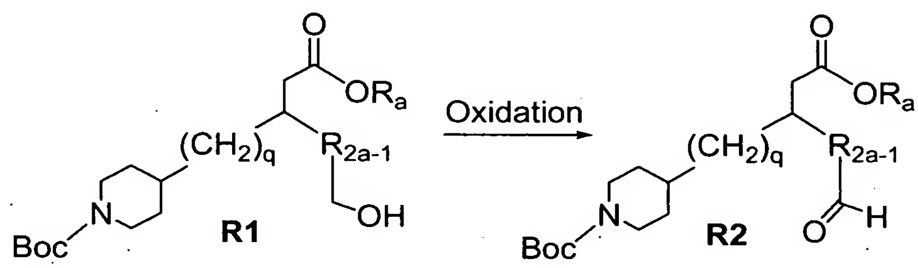


Scheme R

As shown in Scheme R, compounds of the present invention may be made via an intermediate wherein R_{2a} is activated with a terminal aldehyde. The hydroxy substituent of Compound **R1** may be oxidized using conventional oxidation chemistry, such as the Swern oxidation to afford aldehyde Compound **R2**. Compound **R2** may be further elaborated through reductive amination with a suitable amine in the presence of

a hydride source to arrive at compounds wherein R_{2a} and T are linked through an alkylamino linkage. The terminal amino group may be reacted with acid chlorides, formyl chlorides, carbamates, and the like to obtain amide, carbamate, or urea linkages between R_{2a} and T. In addition, Compound **R2** may undergo Wittig chemistry to yield a new carbon bond linkage.

Scheme R



R_{2a-1} = R_2 precursor

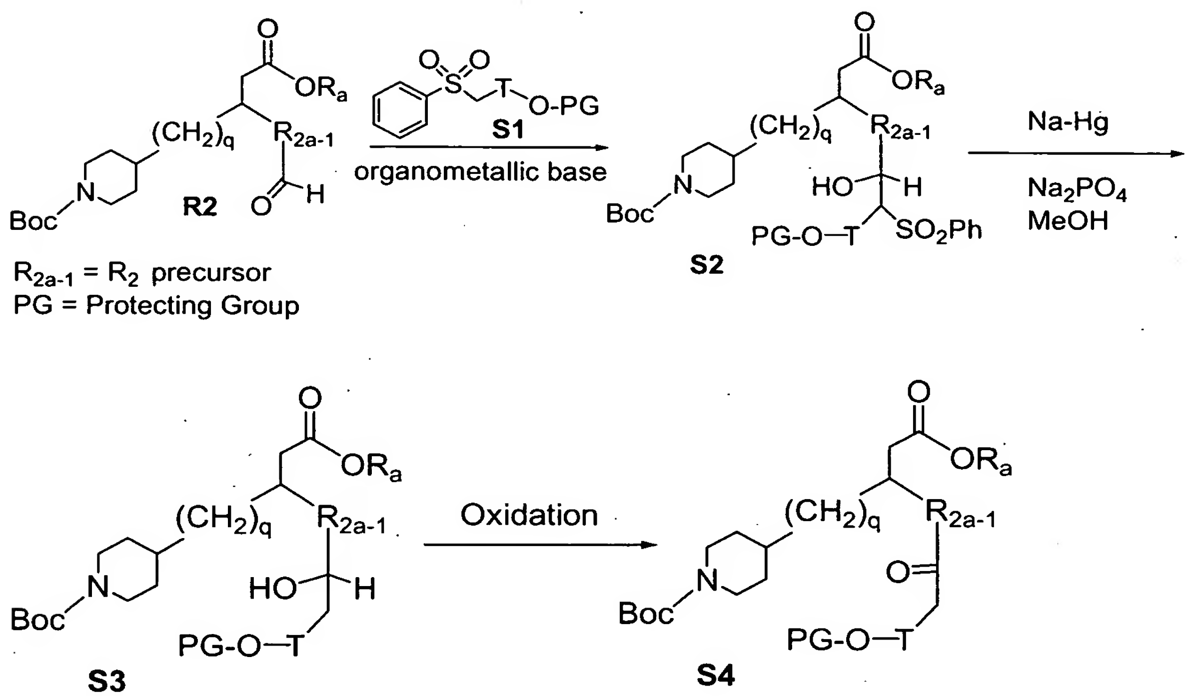
Furthermore, the hydroxy substituent of Compound **R1** may be oxidized to its corresponding carboxylic acid using a strong oxidizing agent, such as Jones reagent or PCC in DMF or the like. The resulting carboxylic acid may take part in a variety of known chemical transformations such as the Curtius rearrangement followed by either hydrolysis or treatment with benzyl alcohol and hydrogenation, leading to compounds wherein R_{2a} is activated with a terminal amino group for further elaboration as discussed herein.

Scheme S

Scheme S describes the preparation of compounds of the present invention. Aldehyde **R2** may be treated with Compound **S1** and an organometallic base such as *n*-butyllithium to provide intermediate Compound **S2**. Subsequent treatment of Compound **S2** with sodium mercury amalgam, aluminum mercury amalgam, or Raney Nickel in aqueous alcoholic solvent results in removal of the phenyl sulfone functionality. Oxidation of Compound **S3** using standard oxidation chemistry affords ketone Compound **S4**. Upon removal of the protecting group, the hydroxy group may be reacted with number of activated precursors of R_{13} possessing functional groups such

as formyl chlorides to make carbonates, isocyanates to afford carbamates, activated esters and the like.

Scheme S



The terminal hydroxy group on T may be oxidized using Swern or Moffat chemistry to afford T functionalized with an aldehyde. The aldehyde may be reductively aminated with precursors to R_{13} activated with amines to form secondary amines, or with precursors to R_{13} activated with acyl hydrazines to form acyl hydrazones.

Furthermore, the terminal hydroxy group on T may be oxidized using conventional chemistry to yield a T with a terminal carboxy group. The terminal carboxy group may be coupled with precursors to R_{13} that possess a hydroxyl functionality to form an ester linkage using standard peptide coupling or esterification methods, such as treatment with DCC and a catalytic amount of DMAP in DMF (Zlatkov, A. et al., *Arch. Pharm* (Weinheim), **1998**, 331 (10), 313-318).

Similarly, the terminal carboxy group on T may be coupled with precursors to R_{13} that possess an amino functionality to form an amide linkage. Typical reagents used for such coupling reactions are PyBroP in DMP with a catalytic amount of DMAP. An alternative method uses BOP with a trialkylamine base in DMP (Scherer, M. et al. *Chem Commun*, **1998**, (1), 85-86; Bendavid, A. et al. *J. Org. Chem.* **2001**, 66 (11), 3709-3718).

Once the group R_{13} has been installed on compounds of the present invention, it is suitably functionalized for incorporated into a pegylated liposome. Several methods have been developed to accomplish this transformation. The least complex method involves the incubation of compounds of Fomula (I) with a fully formed pegylated liposome. With this procedure, compounds of Formula (I) form a micellar suspension in water which, upon addition of pre-formed pegylated liposomes loaded with a certain therapeutic agent, effects the ordered insertion of compounds of Formula (I) into the lipid bilayer of the liposome (Zalipsky, S et al., Bioconjugate Chem. 1997, (8) 111-118). In the insertion process, the phospholipid portion of R_{13} acts as an anchor in the lipid bilayer of the pegylated liposome. The oligomeric PEG portion of R_{13} extends outward from the liposome and serves to display the remainder of the compound of Formula (I) at the interface of the pegylated region of the liposome and the solvent. By controlling the concentration, this composition can be composed of ten to several thousand molecules of a compound of Formula (I) inserted into the bilayer of the pegylated liposome and displayed at the liposome: solvent interface. This incubation is run at temperatures ranging from ambient to 37 °C for up to 48 h.

Another means for the incorporation of compounds of Formula (I) into a liposomal formulation involves mixing compounds of Formula (I) with the appropriate lipid components and forming unilamellar liposomes from this mixture. The method is carried out by dissolving defined proportions of a phospholipid, such as dipalmitoylphosphatidylcholine, cholesterol, a pegylated phospholipid, such as PEG-2000 disteroylphosphatidylethanolamine in chloroform:methanol, and a predetermined measure of a compound of Formula (I). A lipid film is prepared, then hydrated, the therapeutic agent is added and finally extruded several times through polycarbonate

membranes until the liposomes form from the extrusion at the desired size (Lee, R. J.; Low, P. S., Biochim. Biophys. Acta, 1995 (1233) 134-144.

A third method involves forming the liposome by the second method discussed herein substituting a molecule derived from the precursor of R_{13}. The liposome decorated with these reactive head groups on the phospholipid is then capable of reacting with precursors of Formula (I) wherein T is activated with a complementary functional group and the liposome with the reactive phospholipid head groups interact with these intermediates in the same manner as described for Schemes O through S (Lee, R. J., Low, P. S., J. Biol. Chem., 1994, 269 (5), 3198-3204; Gyongyossy-Issa, M.I.C. et al., Arch. Biochem. Biophys., 1998, 353 (1), 101-108).

Specific Synthetic Methods

Specific compounds which are representative of this invention were prepared as per the following examples and reaction sequences; the examples and the diagrams depicting the reaction sequences are offered by way of illustration, to aid in the understanding of the invention and should not be construed to limit in any way the invention set forth in the claims which follow thereafter. The instant compounds may also be used as intermediates in subsequent examples to produce additional compounds of the present invention. No attempt has been made to optimize the yields obtained in any of the reactions. One skilled in the art would know how to increase such yields through routine variations in reaction times, temperatures, solvents and/or reagents.

Reagents were purchased from commercial sources. Microanalyses were performed at Robertson Microlit Laboratories, Inc., Madison, New Jersey and are expressed in percentage by weight of each element per total molecular weight. Nuclear magnetic resonance (NMR) spectra for hydrogen atoms were measured in the indicated solvent with (TMS) as the internal standard on a Bruker Avance (300 MHz) spectrometer. The values are expressed in parts per million downfield from TMS. The mass spectra (MS) were determined on a Micromass Platform LC spectrometer as (ESI) *m/z* ($M+H^+$) using an electrospray technique. Stereoisomeric compounds may be characterized as racemic

mixtures or as separate diastereomers and enantiomers thereof using X-ray crystallography and other methods known to one skilled in the art. Unless otherwise noted, the materials used in the examples were obtained from readily available commercial suppliers or synthesized by standard methods known to one skilled in the art of chemical synthesis. The substituent groups, which vary between examples, are hydrogen unless otherwise noted.

Example 1

1-[[3-[(1,4,5,6-Tetrahydro-2-pyrimidinyl)amino]phenyl]acetyl]-4-piperidinepropanoic acid (Cpd **1**)

Methyl iodide (3.21 mL, 51.6 mmol) was added to a solution of 3,4,5,6-tetrahydro-2-pyrimidinethiol Compound **1a** (6.00 g, 51.6 mmol) in absolute ethanol (45 mL). The mixture was refluxed for 3 h, concentrated and dried *in vacuo* to yield Compound **1b** as a colorless oil. MS (ES+) m/z 172 (M+41). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.89 (m, 2H), 2.61 (s, 3H), 3.61 (m, 4H), 9.56 (s, 1H).

Boc_2O (11.33 g, 51.91 mmol) was added to a solution of Compound **1b** (13.4 g, 51.9 mmol) and TEA (7.23 mL, 51.9 mmol) in DCM (70 mL) at 0 °C and the mixture was stirred at rt for 2 d. The organic layer was washed with water (2x75 mL), dried (Na_2SO_4) and concentrated to give Compound **1c**. MS (ES+) m/z 231 ($M+H^+$).

A solution of Compound **1c** (0.91 g, 3.95 mmol) and 3-aminophenylacetic acid Compound **1d** (0.59 g, 3.95 mmol) in DMA (5 mL) was heated to 80-85 °C for 4 d. The mixture was cooled to rt and diluted with MeCN. The solid was filtered and washed with MeCN and Et_2O, then dried *in vacuo*. Water was added and the pH was adjusted to pH 1-2 by adding conc. HCl dropwise. The resulting solution was lyophilized to give Compound **1e** as a light yellow solid. MS (ES+) m/z 234 ($M+H^+$).

Boc_2O (19 g, 87 mmol) and TEA (13 mL, 96 mmol) were added to a solution of 4-piperidinemethanol Compound **1f** (10 g, 87 mmol), DMAP (catalytic amount), dioxane (90 mL) and water (45 mL) at 5 °C. The reaction mixture was stirred

overnight at rt and diluted with DCM (100 mL). The organic layer was washed with saturated NH_4Cl, dried (Na_2SO_4) and concentrated to give Compound **1g**. MS (ES+) m/z 216 ($M+H^+$).

DMSO (4.28 mL, 60.38 mmol) was added over a 15 min period to a solution of oxalyl chloride (2.63 mL, 30.19 mmol) in DCM (110 mL) at -78 °C. After stirring at -78 °C for 30 min, a solution of Compound **1g** (5.0 g, 23.2 mmol) in DCM (10 mL) was added dropwise. The resulting mixture was stirred at -78 °C for 2 h. TEA (19.42 mL, 139.3 mmol) was added dropwise and the mixture was warmed to rt and quenched with water. The organic layer was separated, washed sequentially with saturated NH_4Cl (75 mL), water (75 mL), saturated $NaHCO_3$ (75 mL) and saturated brine (75 mL), then dried (Na_2SO_4) and concentrated to give Compound **1h**. MS (ES+) m/z 214 ($M+H^+$). ^1H NMR (DMSO-d_6, 300 MHz) δ 1.4 (s, 9H), 1.89 (m, 4H), 2.58 (m, 1H), 3.85 (m, 4H), 9.65 (s, 1H).

A solution of Compound **1h** (2.29 g, 10.7 mmol) in DCM (15 mL) was added dropwise to a solution of carbethoxymethylene triphenylphosphorane (4.11 g, 10.7 mmol) in DCM (20 mL) at 0 °C. The resulting mixture was warmed to rt and stirred overnight. The mixture was concentrated and the residue was purified by flash chromatography (silica gel, 15-30% ethyl acetate/hexane) to give Compound **1i**. MS (ES+) m/z 284 ($M+H^+$). ^1H NMR (DMSO-d_6, 300 MHz) δ 1.2 (t, J = 7 Hz, 3H), 1.39 (s, 9H), 1.69 (m, 2H), 2.36 (m, 1H), 2.74 (m, 2H), 3.94 (m, 2H), 4.11 (q, J = 7 Hz, 2H), 5.86 (d, J = 15 Hz, 2H), 6.82 (dd, J = 15, 7 Hz, 2H).

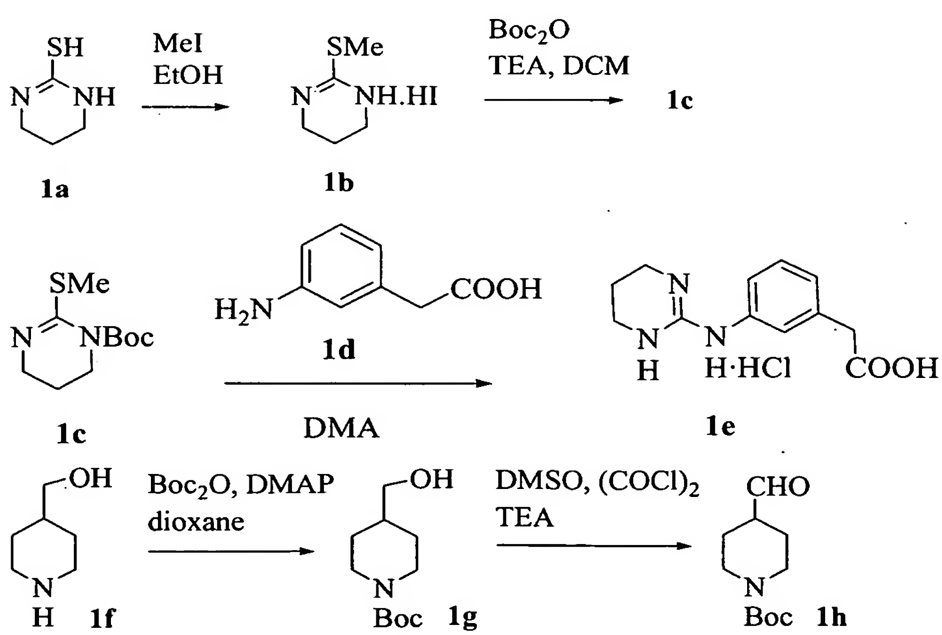
A mixture of Compound **1i** (1.6 g, 5.6 mmol), TFA (10 mL) and anisole (1 drop) in DCM (10 mL) was stirred at rt for 1.5 h. The mixture was concentrated and dried *in vacuo* to give Compound **1j** as a TFA salt. MS (ES+) m/z 184 ($M+H^+$).

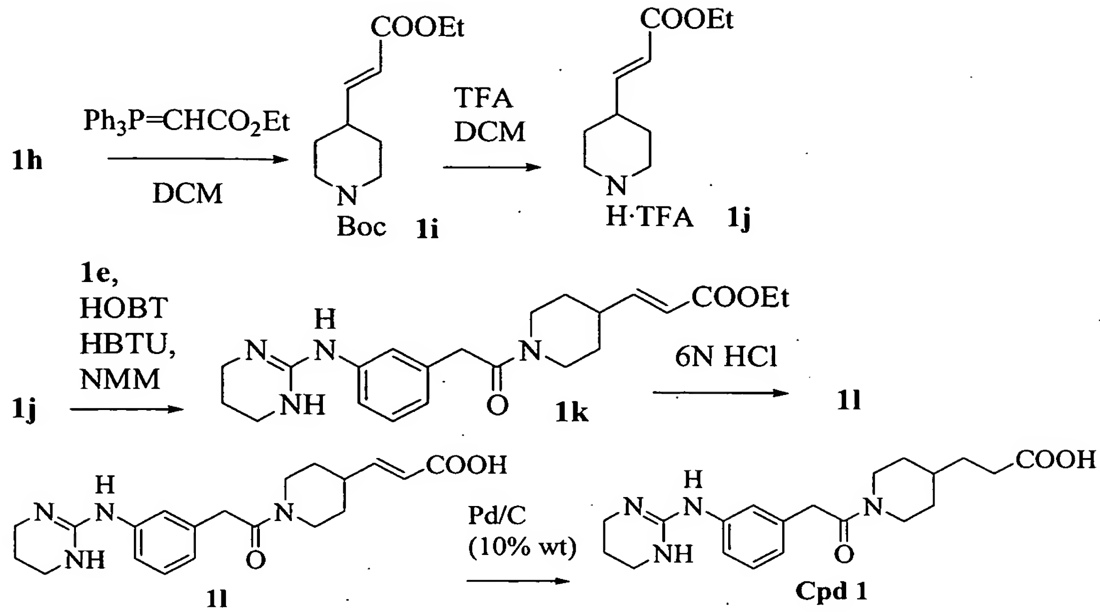
NMM (0.22 mL, 2.07 mmol), Compound **1e** (0.29 g, 1.04 mmol), NMM (0.114 mL, 1.04 mmol), HOBT (0.07g, 0.51 mmol) and HBTU (0.46 g, 1.24 mmol) were added sequentially to a solution of Compound **1j** (0.308 g, 1.04 mmol) in MeCN (20 mL) and DMF (2 mL). The mixture was stirred at 0 °C for 1 h, then at rt overnight, quenched

with saturated NH_4Cl, concentrated and extracted with EtOAc. The organic layer was dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography (silica gel, 10%EtOH/1.5%NH_4OH/DCM to16% EtOH/1.5% NH_4OH/DCM) to yield Compound **1k** as a colorless solid. MS (ES+) m/z 399 ($M+H^+$).

Compound **1k** (0.27 g) was dissolved in ice cold 6N HCl (20 mL) at 0 °C and stirred at rt for 2 d. The mixture was concentrated and MeCN (3x20 mL) was used as an azeotrope. The resulting solid was triturated with Et_2O and DCM and purified by RP-HPLC (10-90% MeCN/water, 0.1% TFA) to yield Compound **1l** as a TFA salt. MS (ES+) m/z 371 ($M+H^+$). ^1H NMR (DMSO-d_6, 300 MHz) δ 1.07 (m, 2H), 1.65 (m, 4H), 1.7 (m, 2H), 2.41 (m, 1H), 3.05 (m, 2H), 3.72 (s, 2H), 3.91 (m, 2H), 4.37 (m, 2H), 5.74 (d, J = 16 Hz, 1H), 6.75 (m, 1H), 7.15 (m, 3H), 7.42 (m, 1H), 8.15 (br s, 1H), 9.76 (s, 1H). Anal. Calcd for $C_{20}H_{26}N_4O_3$-1.57CF_3COOH-0.38H_2O: C, 49.96; H, 5.14; N, 10.08; F, 16.09; H_2O, 1.24. Found: C, 49.62; H, 5.00; N, 9.97; F, 15.98; H_2O, 1.25.

10% Palladium on carbon (85 mg) was added to a solution of Compound **1l** (0.05 g) in warm EtOH (10 mL) under argon and the mixture was hydrogenated (40 psi) in a Parr apparatus. The mixture was filtered through celite and concentrated at reduced pressure to yield Compound **1** as a sticky solid. MS (ES+) m/z 373 ($M+H^+$).





<u>Example 2</u>

1-[1-Oxo-3-[3-[(1,4,5,6-tetrahydro-2-pyrimidinyl)amino]phenyl]propyl]-4-piperidinepropanoic acid (Cpd **2**)

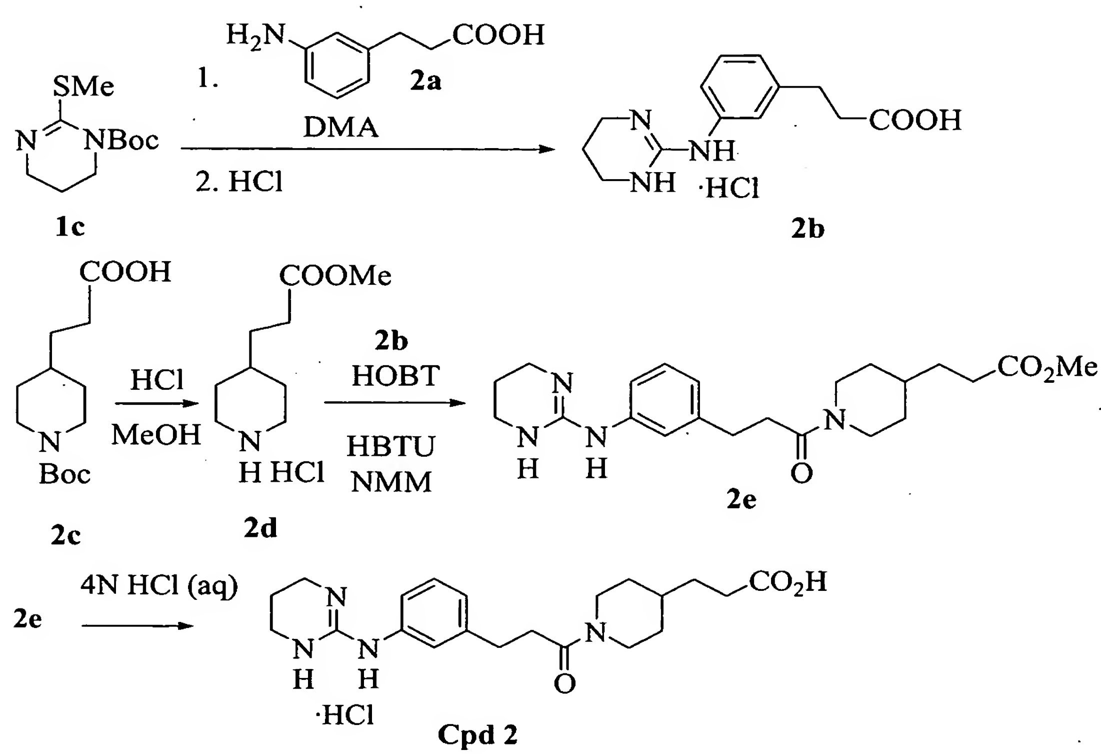
Compound **1c** (0.84 g, 3.65 mmol) was added to a solution of 3-(3-aminophenyl)propionic acid Compound **2a** (0.60 g, 3.65 mmol) in DMA (5 mL). The reaction mixture was stirred at 80-85 °C for 3 d, cooled to rt, diluted with MeCN (30 mL) and filtered. Water was added to the filtrate and the pH was adjusted to 1-2 by adding conc. HCl dropwise. The resulting solution was lyophilized to yield Compound **2b**. MS (ES+) m/z 248 ($M+H^+$).

A solution of 4N HCl in dioxane (8 mL) was added dropwise to a solution of Compound **2c** (1.0 g, 3.9 mmol) in MeOH (20 mL) at 0 °C. The resulting mixture was stirred overnight at rt and concentrated using MeCN (3x20 mL) as an azeotrope. The solid was triturated with Et_2O and hexane, dissolved in water and lyophilized to yield Compound **2d** as a colorless solid. MS (ES+) m/z 172 ($M+H^+$).

NMM (0.23 mL, 2.11 mmol) was added to a solution of Compound **2d** (0.20 g, 0.70 mmol) in MeCN (25 mL) and DMF (2 mL). Compound **2b** (0.15 g, 0.70 mmol), NMM (0.15 mL, 1.40 mmol), HOBT (0.05 g, 0.35 mmol) and HBTU (0.32 g, 0.84 mmol)

were then added and the mixture was stirred for 1 h at 0 °C, followed by overnight at rt. Saturated NH_4Cl was added and the reaction mixture was concentrated and extracted with EtOAc (25 mL). The organic layer was dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude mixture was purified by RP-HPLC (10-90% MeCN/water, 0.1% TFA) to yield Compound **2e**. MS (ES+) m/z 401 ($M+H^+$).

Compound **2e** (0.21 g) was dissolved in 4N HCl (20 mL) at 0 °C and the mixture was stirred overnight at rt. The mixture was concentrated using MeCN (3 x 25 mL) as an azeotrope and triturated with Et_2O to yield Compound **2** as an HCl salt. MS (ES+) m/z 387 ($M+H^+$). ^1H NMR (DMSO-d_6, 300 MHz) δ 0.93 (m, 4H), 1.46 (m, 4H), 1.67 (s, 1H), 1.88 (m, 2H), 2.25 (m, 2H), 2.66 (m, 2H), 2.82 (m, 4H), 3.39 (m, 2H), 3.82 (d, J = 13 Hz, 1H), 4.39 (d, J = 13 Hz, 1H), 7.15 (m, 3H), 7.39 (m, 1H), 7.97 (br s, 1H), 9.45 (br s, 1H). Anal. Calcd for $C_{21}H_{30}N_4O_3$-1.85 HCl-1.15 H_2O: C, 53.14; H, 7.26; N, 11.82; H_2O, 4.37. Found: C, 53.19; H, 7.14; N, 11.91; H_2O, 4.62.



Example 3

β-[1-[[3-[(1,4,5,6-Tetrahydro-5-hydroxy-2-pyrimidinyl)amino]phenyl]acetyl]-4-

piperidinyl]-3-quinolinepropanoic acid (Cpd **3**)

N,O-Dimethylhydroxylamine hydrochloride (98%, 2.55 g, 26.17 mmol), NMM (14.39 mL, 130.8 mmol), HOBT (1.47 g, 10.90 mmol) and HBTU (9.83 g, 26.16 mmol) were added to a solution of Compound **3a** (5.00 g, 21.80 mmol) in MeCN (75 mL). The mixture was stirred for 1 h at 0 °C and overnight at rt, quenched with saturated NH_4Cl, concentrated and extracted with EtOAc (3x75 mL). The organic layer was dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was purified by flash column chromatography (silica gel, 30-60% ethyl acetate/hexane with a few drops of TEA) to give Compound **3b** as a liquid. MS (ES+) m/z 273 ($M+H^+$).

n-BuLi (2.5M in hexane, 7.34 mL, 18.35 mmol) was added dropwise to a stirred solution of 3-bromoquinoline (3.81 g, 18.35 mmol) in anhydrous Et_2O (65 mL) at -78 °C over a period of 30 min. The mixture was stirred at -78 °C for 30 min and a solution of Compound **3b** (1.0 g, 3.67 mmol) in Et_2O (20 mL) was added dropwise over a period of 10 min. The resulting mixture was stirred for 30 min -78 °C and allowed to warm to rt. After stirring for 2 h at rt, the mixture was quenched with a saturated NH_4Cl solution and diluted with EtOAc. The organic layer was washed with brine, dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified via chromatography (silica gel, 15-25% ethyl acetate/hexane) to give Compound **3c** as a liquid. MS (ES+) m/z 341 ($M+H^+$).

A solution of NaHMDS (1M, 3.17 mL, 3.17 mmol) in THF was added over a period of 15 min to a stirred solution of trimethyl phosphonoacetate (0.51 mL, 3.17 mmol) in THF (15 mL) at 0 °C under argon. After the resulting mixture was stirred for 20 min, a solution of Compound **3c** (0.27 g, 0.79 mmol) in THF (3 mL) was added over a period of 15 min. The mixture was stirred at 0 °C for 30 min, refluxed for 2.5 h, cooled to rt, diluted with Et_2O (30 mL) and washed with a saturated $NaHCO_3$ solution (2x25 mL) and brine (2x25 mL). The aqueous layer was extracted with Et_2O and the combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by flash column chromatography (silica gel, 10-30% ethyl acetate/hexane) to give Compound **3d** as a mixture of *E*- and *Z*-isomers. MS (ES+) m/z 397 ($M+H^+$).

A mixture of the *E*- and *Z*-isomers of Compound **3d** (0.25 g, 0.63 mmol) and 10% Pd/C (0.12 g) in MeOH (15 mL) was shaken overnight under hydrogen pressure (5 psi) in a Parr apparatus. The mixture was filtered through celite and concentrated under vacuum. The crude product was purified by flash chromatography (70% ethyl acetate in hexane) to yield Compound **3e** as an oil. MS (ES+) m/z 399 ($M+H^+$). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.38 (m, 4H), 1.41 (s, 9H), 1.80 (m, 1H), 2.53 (m, 2H), 3.18 (m, 2H), 3.51 (s, 3H), 3.71 (m, 1H), 4.13 (m, 2H), 7.54 (t, J = 8 Hz, 1H), 7.69 (t, J = 8 Hz, 1H), 7.80 (d, J = 8 Hz, 1H), 7.89 (s, 1H), 8.09 (d, J = 8 Hz, 1H), 8.75 (s, 1H).

Compound **3e** (0.11 g) was dissolved in dioxane (3 mL), one drop of anisole was added and 4N HCl in dioxane (3 mL) was added dropwise. The mixture was stirred at rt for 2 h and concentrated using MeCN as an azeotrope. The resulting solid was triturated with Et_2O and hexane and dried to give Compound **3f** as a sticky solid. MS (ES+) m/z 299 ($M+H^+$). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.34 (m, 4H), 1.94 (m, 1H), 2.67 (m, 2H), 3.01 (m, 2H), 3.24 (m, 2H), 3.43 (s, 3H), 3.68 (m, 1H), 7.79 (t, J = 8 Hz, 1H), 7.94 (t, J = 8 Hz, 1H), 8.13 (d, J = 8 Hz, 1H), 8.23 (d, J = 8 Hz, 1H), 8.48 (m, 1H), 8.70 (m, 1H). Anal. Calcd for $C_{18}H_{22}N_2O_2$-2.2 TFA-0.4H_2O: C, 48.36; H, 4.53; N, 5.04; F, 22.54. Found: C, 48.24; H, 4.42; N, 4.99; F, 22.56.

1,3-Diamino-2-hydroxypropane Compound **3i** (10.0 g, 111 mmol) was dissolved in ethanol (30 mL) and deionized water (30 mL). Carbon disulfide (6.67 mL, 110.95 mmol) was added dropwise *via* an addition funnel over a period of 35 min while the temperature was maintained at 25-33 °C to afford a milky white mixture. The resulting mixture was refluxed for 2 h to afford a yellow solution. After cooling the mixture in ice water, concentrated HCl (7 mL) was added dropwise while maintaining the mixture's temperature at 25-26 °C. The temperature of the mixture was then raised to 79 °C. After stirring for 21 h, the mixture was cooled to 2 °C and filtered *via* vacuum filtration. A white solid was collected, washed three times with a 1:1 mixture of cold ethanol and water and dried *in vacuo* at 40 °C to give Compound **3j**. MS (ES^+) m/z 174 (M^+MeCN). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.96 (d, J = 15 Hz, 2H), 3.15 (d, J = 13 Hz, 2H), 3.33 (m, 1H), 3.89 (m, 1H).

Methyl iodide (2.9 mL, 46 mmol) was added to a stirred solution of Compound **3j** (6.1 g, 46 mmol) in absolute ethanol (35 mL) and the mixture was refluxed for 1 h and cooled to rt. After concentration, the residue was triturated with Et_2O and dried *in vacuo* to give Compound **3k** as a white solid. MS (ES^+) m/z 188 (M+MeCN). ^1H NMR (DMSO-d_6, 300 MHz) δ 2.59 (s, 3H), 3.23 (d, J = 13 Hz, 2H), 3.43 (d, J = 13 Hz, 2H), 4.16 (m, 1H).

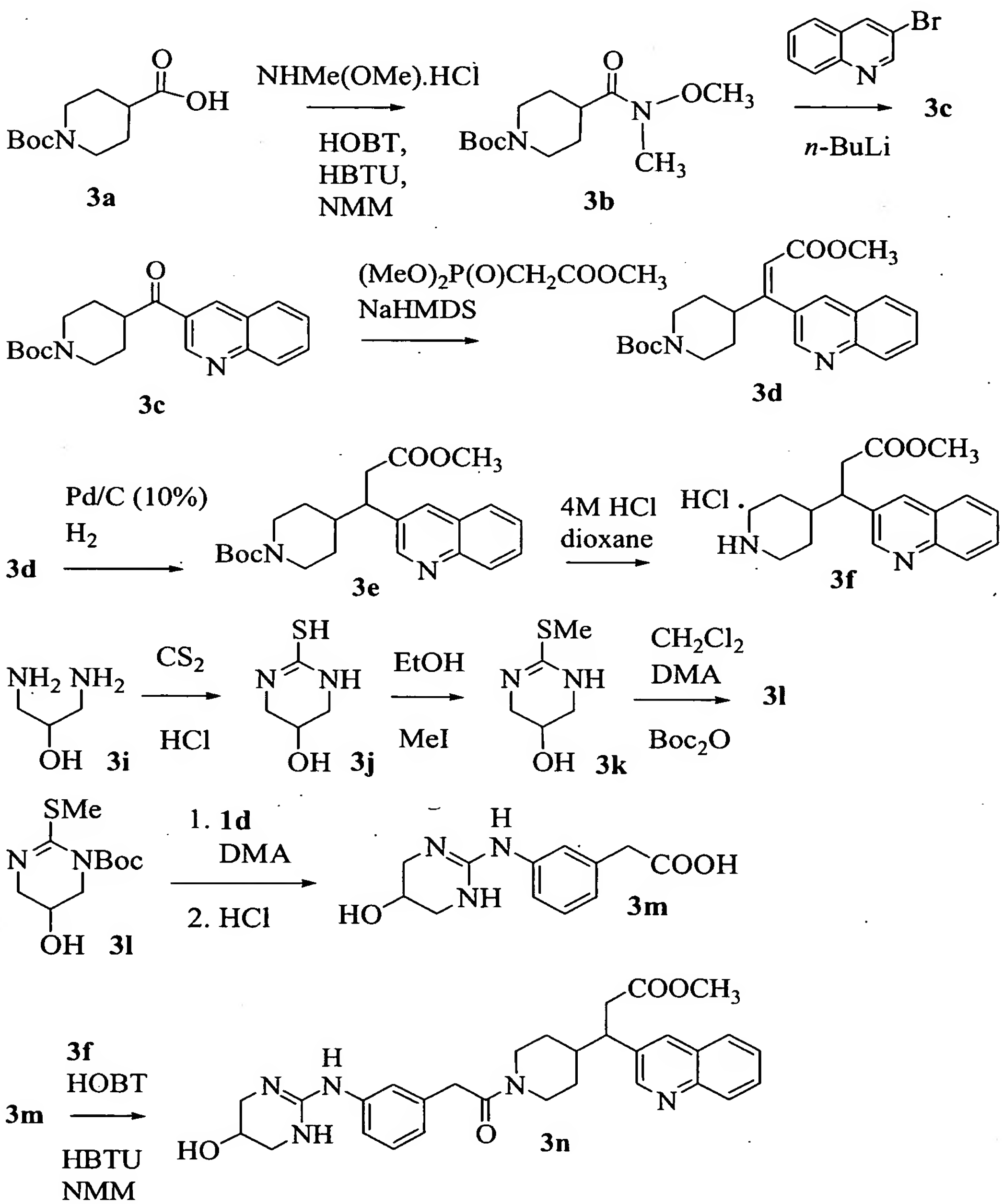
TEA (6.91 mL, 49.61 mmol) was added to a solution of Compound **3k** (13.06 g, 49.61 mmol) in DCM (50 mL) and DMA (5 mL). The mixture was cooled in an ice bath and Boc_2O (10.82 g, 49.61 mmol) was added at 4 °C. The mixture was heated at 41-43 °C for 18 h to afford a light yellow solution. The resulting solution was washed with water (3x75 mL), dried (Na_2SO_4) and concentrated *in vacuo* to yield Compound **3l** as a solid. MS (ES+) m/z 247(M+H^+). ^1H NMR (DMSO-d_6, 300 MHz) δ 1.46 (s, 9H), 1.95 (s, 3H), 2.14 (m, 2H), 2.94 (m, 2H), 3.51 (m, 1H).

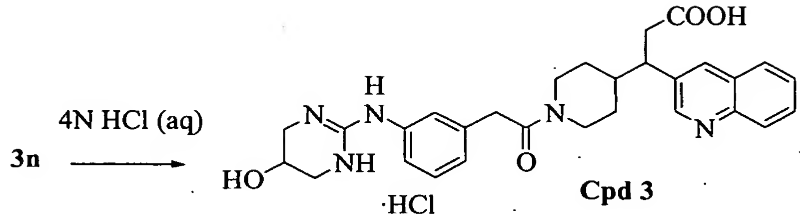
3-Aminophenyl acetic acid Compound **1d** (2.60 g, 17.25 mmol) was added to a solution of Compound **3l** (5.1 g, 21 mmol) in DMA (5 mL). The mixture was heated at 100 °C for 2 d, cooled to rt and diluted with MeCN (75 mL). The resulting precipitate was filtered and washed with MeCN and Et_2O, taken up in water and acidified with conc. HCl. After lyophilization, Compound **3m** was obtained as a white solid. MS (ES+) m/z 250 (M+H^+). ^1H NMR (DMSO-d_6, 300 MHz) δ 3.16 (d, J = 13 Hz, 2H), 3.33 (d, J = 13 Hz, 2H), 3.59 (s, 2H), 7.12 (m, 3H), 7.35 (m, 1H), 8.14 (s, 1H).

Using the procedure described in Example 2 for converting Compound **2d** to Compound **2e**, Compound **3m** was converted to provide Compound **3n** as a solid. MS (ES+) m/z 530 (M+H^+). ^1H NMR (DMSO-d_6, 300 MHz) δ 0.92 (m, 4H), 1.33 (m, 2H), 1.90 (m, 1H), 2.88 (m, 4H), 3.17 (m, 3H), 3.33 (m, 2H), 3.43 (s, 3H), 4.06 (m, 2H), 4.32 (m, 1H), 6.98 (m, 3H), 7.27 (m, 1H), 7.48 (m, 1H), 7.66 (m, 1H), 7.79 (m, 1H), 8.01 (m, 3H), 8.25 (br s, 1H), 8.83 (br s, 1H).

Using the procedure described in Example 2 for converting Compound **2e** to

Compound **2**, Compound **3n** was converted to provide Compound **3** as a solid. MS (ES+) m/z 516 ($M+H^+$). ^1H NMR (DMSO-d_6, 300 MHz) δ 0.92 (m, 4H), 1.33 (m, 1H), 1.90 (m, 2H), 2.88 (m, 4H), 3.17 (m, 1H), 3.33 (m, 4H), 4.06 (m, 2H), 4.32 (m, 1H), 6.98 (m, 3H), 7.24 (m, 1H), 7.77 (m, 1H), 7.72 (m, 1H), 8.03 (m, 1H), 8.10 (m, 1H), 8.18 (m, 1H), 8.65 (m, 1H), 9.21 (br s, 1H).





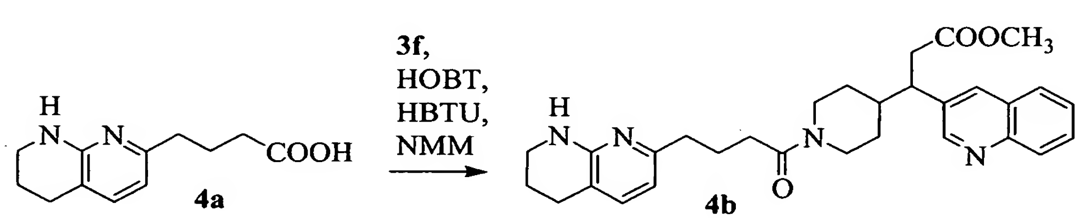
Cpd 3

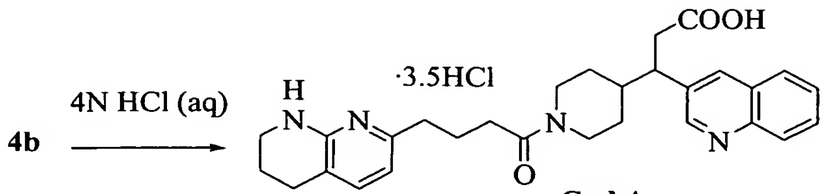
Example 4

β-[1-[1-Oxo-4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl]-4-piperidinyl]-3-quinolinepropanoic acid (Cpd **4**)

Compound **4a** was prepared as described in WO 99/31061. Using the procedure described in Example 2 for converting Compound **2d** to Compound **2e**, Compound **4a** was converted and purified by RP-HPLC (10-70% acetonitrile/water, 0.1% TFA) to provide Compound **4b**. MS (ES+) m/z 501 ($M+H^+$). ^1H NMR (DMSO-d_6, 300 MHz) δ 1.02 (m, 4H), 1.33 (m, 1H), 2.86 (m, 4H), 2.29 (m, 2H), 2.61 (m, 2H) 2.72 (m, 2H), 2.86 (m, 2H), 2.98 (m, 2H), 3.17 (m, 1H), 3.44 (s, 3H), 3.78 (m, 2H), 4.35 (m, 2H), 6.52 (d, J = 7 Hz, 1H), 7.56 (d, J = 7 Hz, 1H), 7.78 (m, 2H), 7.99 (m, 2H), 8.41 (s, 1H), 8.91 (s, 1H).

Using the procedure described in Example 2 for converting Compound **2e** to Compound **2**, Compound **4b** was converted to provide Compound **4** as a sticky solid. MS (ES+) m/z 487 ($M+H^+$). ^1H NMR (DMSO-d_6, 300 MHz) δ 0.99 (m, 4H), 1.49 (m, 1H), 2.86 (m, 4H), 2.30 (m, 2H), 2.69 (m, 2H), 2.81 (m, 1H), 2.92 (m, 2H), 3.13 (m, 2H), 3.33 (m, 1H), 3.79 (m, 2H), 4.41 (m, 2H), 6.55 (d, J = 7 Hz, 1H), 7.56 (d, J = 7 Hz, 1H), 7.86 (m, 1H), 7.98 (m, 2H), 8.72 (m, 2H), 8.83 (s, 1H), 9.15 (s, 1H). Anal. Calcd for $C_{29}H_{34}N_4O_3$-3.5 HCl-H_2O: C, 55.09; H, 6.30; N, 8.86; H_2O, 3.24. Found: C, 54.83; H, 6.53; N, 9.08; H_2O, 3.24.





Cpd 4

Using the procedure of Example 4 and the appropriate reagents and starting materials known to those skilled in the art, other compounds of the present invention may be prepared including, but not limited to:

Cpd	Name	MS (m/z)
14	β-(1,3-benzodioxol-5-yl)-1-[1-oxo-3-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)propyl]-4-piperidinepropanoic acid	466
15	β-(1,3-benzodioxol-5-yl)-1-[1-oxo-4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl]-4-piperidinepropanoic acid	480
16	β-(1,3-benzodioxol-5-yl)-1-[(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)acetyl]-4-piperidinepropanoic acid	452
17	6-methoxy-β-[1-[1-oxo-4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl]-4-piperidinyl]-3-pyridinepropanoic acid	467
82	3-(2,3-Dihydro-benzofuran-6-yl)-3-[1-4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl]-4-piperidinyl]-propanoic acid	

and pharmaceutically acceptable salts thereof.

Example 5

1,2,3,4-Tetrahydro-β-[1-[1-oxo-4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl]-4-piperidinyl]-3-quinolinepropanoic acid (Cpd **5**)

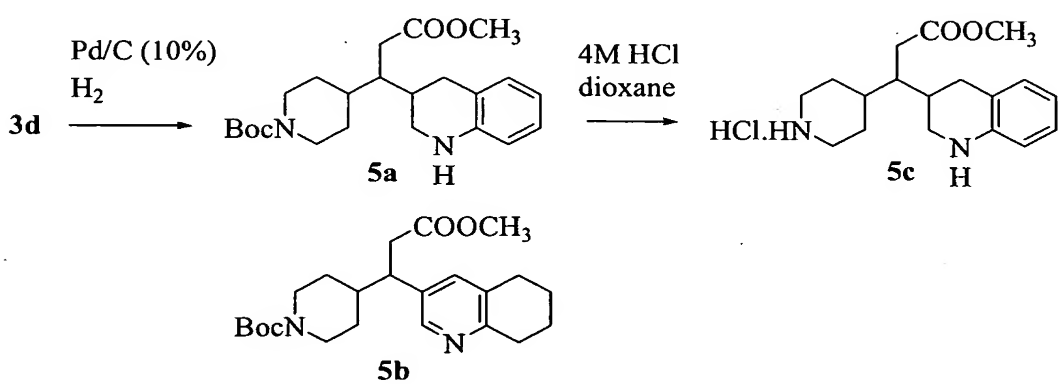
Compound **3d** (0.49 g) was combined with 10% Pd/C (0.6 g) in methanol (40 mL) and water (1.5 mL), and hydrogenated at 50 psi of H_2 for 3 d. After filtration of catalyst, the evaporated material was purified by flash chromatography (gradient 20-30% ethyl acetate in heptane with a few drops of triethylamine) to provide Compounds **5a** (0.23 g, 47%) and **5b** (0.16 g, 32%). Cpd **5a**: MS (ES+) m/z 403 ($M+H^+$). ^1H NMR ($CDCl_3$, 300 MHz) δ 1.2-1.7 (m, 4H), 1.45 (s, 9H), 1.9-2.4 (m, 4H), 2.5-3.1 (m, 5H), 3.27 (m, 1H), 3.68 (s, 3H), 3.84 (m, 1H), 4.13 (m, 2H), 6.48 (d, J = 8 Hz, 1H), 6.61-6.69 (m,

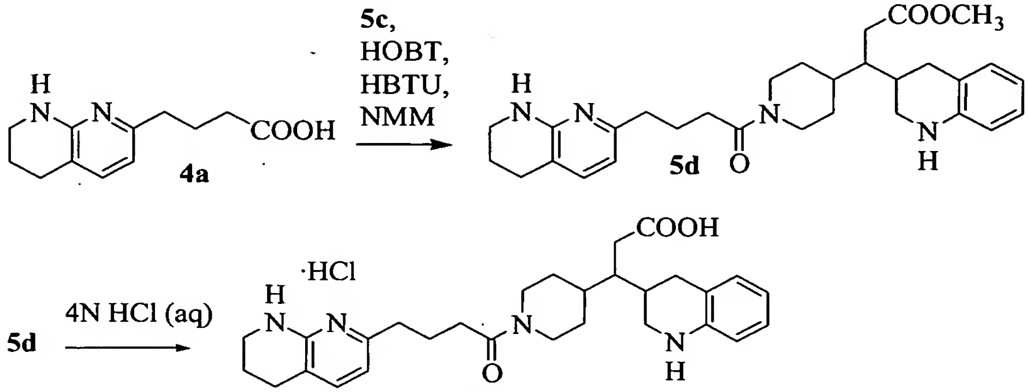
1H), 6.92-6.99 (m, 2H). Cpd **5b**: MS (ES+) m/z 403.5 (M+H$^+$). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 0.8-1.3 (m, 4H), 1.35 (s, 9H), 1.6-1.8 (m, 4H), 2.6-2.8 (m, 10H), 3.45 (s, 3H), 3.8-4.0 (m, 2H), 7.27 (m, 1H), 8.08 (m, 1H).

Using the procedure described in Example 3 for converting Compound **3e** to Compound **3f**, Compound **5a** was converted to provide Compound **5c** as a solid. MS (ES+) m/z 303 (M+H$^+$). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.61 (m, 4H), 1.82 (m, 1H), 2.32 (m, 1H), 2.44 (m, 2H), 2.78 (m, 2H), 3.25 (m, 2H), 3.35 (m, 2H), 3.62 (s, 3H), 3.78 (m, 3H), 7.16 (m, 2H), 8.76 (m, 2H).

Using the procedure described in Example 2 for converting Compound **2d** to Compound **2e**, Compound **4a** was reacted with Compound **5c** and purified by RP-HPLC (10-70% acetonitrile/water, 0.1% TFA) to provide Compound **5d**. MS (ES+) m/z 505 (M+H$^+$). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.11 (m, 4H), 1.56 (m, 1H), 1.79 (m, 6H), 2.32 (m, 4H), 2.66 (m, 2H), 2.77 (m, 2H), 2.91 (m, 2H), 3.16 (m, 2H), 3.5 (m, 2H), 3.62 (s, 3H), 3.82 (m, 2H), 4.43 (m, 2H), 6.58 (m, 3H), 7.63 (d, J = 7 Hz, 1H), 7.93 (m, 2H).

Using the procedure described in Example 2 for converting Compound **2e** to Compound **2**, Compound **5d** was converted to provide Compound **5** as an HCl salt. MS (ES+) m/z 491 (M+H$^+$). ^{1}HNMR (DMSO-d_6, 300 MHz) δ 1.13 (m, 4H), 1.54 (m, 2H), 1.77 (m, 4H), 2.21 (m, 4H), 2.37 (m, 1H), 2.64 (m, 2H), 2.71 (m, 2H), 2.96 (m, 2H), 3.23 (m, 2H), 3.45 (s, 2H), 3.84 (m, 2H), 4.45 (m, 2H), 6.54 (m, 3H), 6.98 (m, 2H), 7.61 (d, J = 8 Hz, 1H), 8.01 (br s, 1H).





Cpd 5

Using the procedure of Example 5 and the appropriate reagents and starting materials known to those skilled in the art, other compounds of the present invention may be prepared including, but not limited to:

Cpd	Name	MS (m/z)
18	1,4,5,6-tetrahydro-2-methyl-β-[[1-[1-oxo-3-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)propyl]-4-piperidinyl]methyl]-5-pyrimidinepropanoic acid	456
19	1,2,3,4-tetrahydro-β-[[1-[1-oxo-3-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)propyl]-4-piperidinyl]methyl]-3-quinolinepropanoic acid	491
57	5,6,7,8-tetrahydro-β-[[1-[1-oxo-3-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)propyl]-4-piperidinyl]methyl]-3-quinolinepropanoic acid	491

and pharmaceutically acceptable salts thereof.

Example 6

β-[2-[1-[3-[(1,4,5,6-Tetrahydro-2-pyrimidinyl)amino]benzoyl]-4-piperidinyl]ethyl]-3-pyridinepropanoic acid (Cpd **6**)

Using the procedure described in Example 3 for converting Compound **3a** to

Compound **3b**, *N*-Boc-piperidin-4-propionic acid Compound **2c** was converted to Compound **6a** (colorless liquid; purified by flash chromatography (on silica gel, eluted with 30-50% ethyl acetate/hexane with a few drops of TEA). MS (ES+) m/z 301 ($M+H^+$). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.14 (m, 4H), 1.45 (s, 9H), 1.62 (m, 1H), 1.68 (m, 2H), 2.44 (t, J = 7.5 Hz, 2H), 2.63 (m, 2H), 3.18 (s, 3H), 3.68 (s, 3H), 4.08 (m, 2H).

Using the procedure described in Example 3 for converting Compound **3b** to Compound **3c**, Compound **6a** was converted to Compound **6b** (purified by flash chromatography on silica gel, eluted with 30-50% ethyl acetate/hexane with a few drops of TEA). MS (ES+) m/z 319 ($M+H^+$).

Using the procedure described in Example 3 for converting Compound **3c** to Compound **3d**, Compound **6b** was converted to Compound **6c** (purified by flash chromatography on silica gel, eluted with 30-50% ethyl acetate/hexane with a few drops of TEA). MS (ES+) m/z 375 ($M+H^+$).

Using the procedure described in Example 3 for converting Compound **3d** to Compound **3e**, Compound **6c** was converted to Compound **6d** (purified by flash chromatography on silica gel, eluted with 15-35% ethyl acetate/hexane with a few drops of TEA). MS (ES+) m/z 377 ($M+H^+$). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 0.91 (m, 4H), 1.12 (m, 2H), 1.29 (m, 1H), 1.41 (s, 9H), 1.53 (m, 3H), 2.63 (m, 2H), 3.98 (m, 2H), 3.35 (s, 3H), 3.48 (m, 1H), 3.88 (m, 2H), 7.34 (m, 1H), 7.68 (m, 1H), 8.43 (m, 2H).

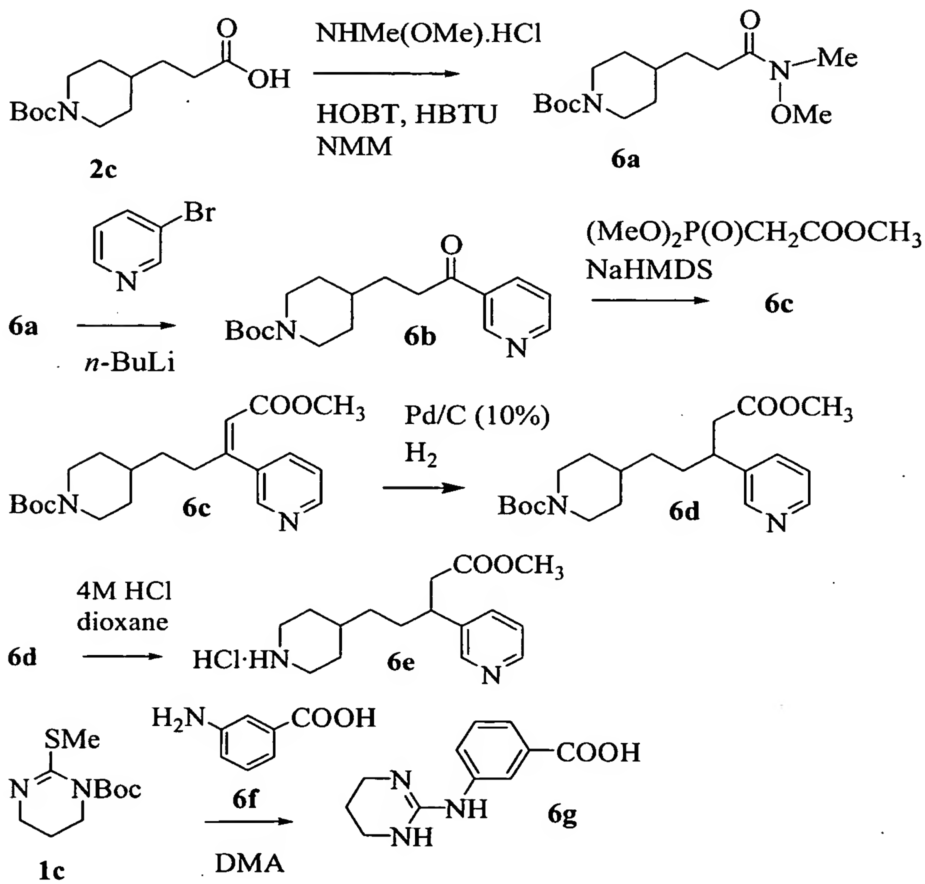
Using the procedure described in Example 3 for converting Compound **3e** to Compound **3f**, Compound **6d** was converted to Compound **6e** (white solid). MS (ES+) m/z 277 ($M+H^+$). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 0.91 (m, 2H), 1.19 (m, 4H), 1.44 (m, 1H), 1.71 (m, 2H), 2.71 (m, 2H), 2.82 (m, 2H), 3.08 (m, 2H), 3.21 (m, 1H), 3.49 (s, 3H), 7.51 (m, 1H), 7.94 (m, 1H), 8.53 (m, 2H).

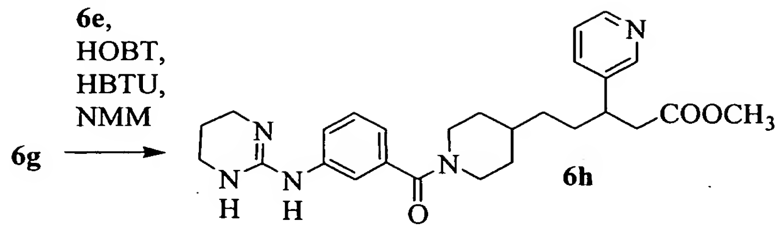
Using the procedure described in Example 1 for converting Compound **1c** to

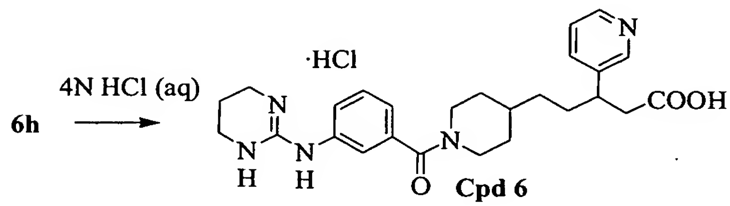
Compound **1e**, Compound **1c** was reacted with 3-aminobenzoic acid Compound **6f** to provide Compound **6g** as a white amorphous solid. MS (ES+) m/z 220 (M+H$^+$). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 4.13 (m, 2H), 5.42 (t, J = 5 Hz, 4H), 6.81 (m, 4H).

Using the procedure described in Example 1 for converting Compound **1j** to Compound **1k**, Compound **6g** was reacted with Compound **6e** to produce Compound **6h** (purified via RP-HPLC: 5-50% acetonitrile/water, 0.1% TFA). MS (ES+) m/z 478 (M+H$^+$).

Using the procedure described in Example 2 for converting Compound **2e** to Compound **2**, Compound **6h** was converted to Compound **6** (purified via RP-HPLC: 5-50% acetonitrile/water, 0.1% TFA). MS (ES+) m/z 464 (M+H$^+$). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.11 (m, 2H), 1.19 (m, 2H), 1.49 (m, 4H), 1.68 (m, 1H), 1.72 (m, 4H), 2.72 (m, 4H), 3.15 (m, 1H), 3.65 (m, 2H), 4.38 (m, 2H), 7.12-7.51 (m, 4H), 7.73 (m, 1H), 8.21 (m, 1H), 8.65 (m, 2H).







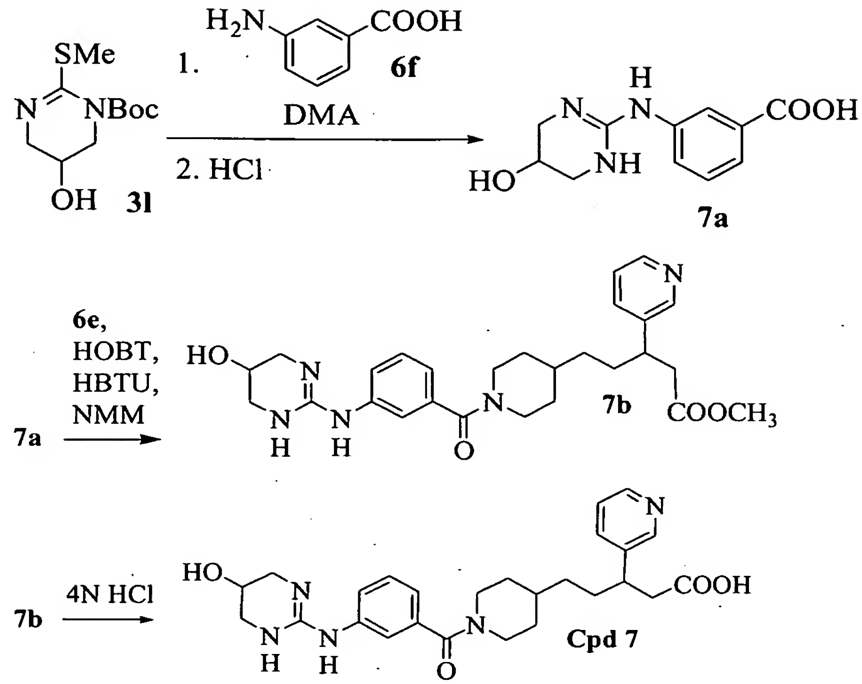
Example 7

β-[2-[1-[3-[(1,4,5,6-Tetrahydro-5-hydroxy-2-pyrimidinyl)amino]benzoyl]-4-piperidinyl]ethyl]-3-pyridinepropanoic acid (Cpd 7)

Using the procedure described in Example 3 for converting Compound **3l** to Compound **3m**, Compound **3l** was reacted with 3-aminobenzoic acid Compound **6f** to provide Compound **7a** as a white amorphous solid. MS (ES+) m/z 235 ($M+H^+$). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 3.18 (d, J = 12 Hz, 2H), 3.35 (d, J = 12 Hz, 2H), 4.09 (m, 1H), 7.55 (m, 2H), 7.84 (m, 2H).

Using the procedure described in Example 3 for converting Compound **3m** to Compound **3n**, Compound **7a** was reacted with Compound **6e** to produce Compound **7b** (white solid; purified by RP-HPLC: 2-30% acetonitrile/water, 0.1% TFA). MS (ES+) m/z 494 ($M+H^+$).

Using the procedure described in Example 3 for converting Compound **3n** to Compound **3**, Compound **7b** was converted to provide Compound **7** as a white solid. MS (ES+) m/z 480 ($M+H^+$). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.03 (m, 2H), 2.22 (m, 4H), 1.49 (m, 1H), 1.66 (m, 2H), 2.65 (m, 2H), 2.76 (m, 2H), 3.06 (m, 2H), 3.18 (m, 4H), 3.34 (m, 1H), 4.13 (s, 1H), 7.12-8.78 (m, 8H), 9.91 (s, 1H).



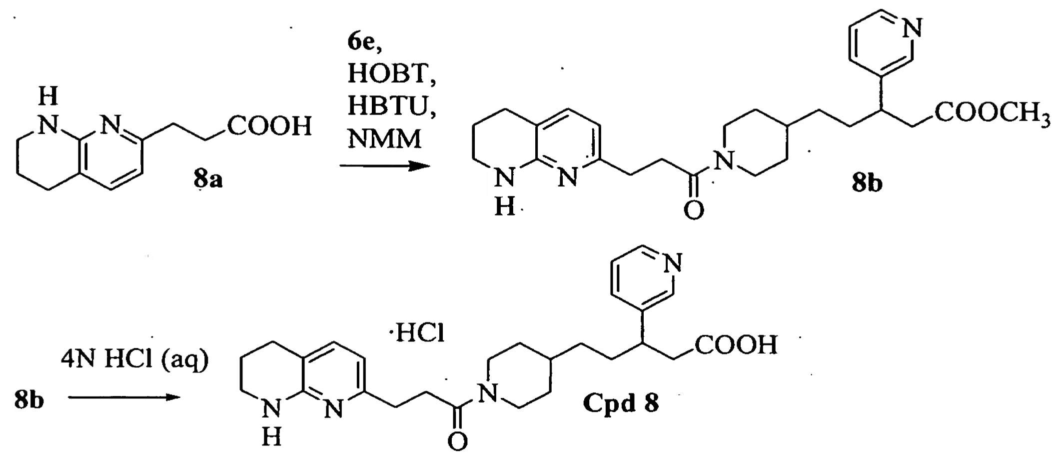
Example 8

β-[2-[1-[1-Oxo-3-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)propyl]-4-piperidinyl]ethyl]-3-pyridinepropanoic acid (Cpd **8**)

The acid Compound **8a** was derived from the corresponding ethyl ester as described in WO99/31061, the synthesis of which was described in WO 00/72801.

Using the procedure described in Example 5 for converting Compound **4a** to Compound **5c**, Compound **8a** was reacted with Compound **6e** to yield Compound **8b** (purified by RP-HPLC: 10-90% acetonitrile/water, 0.1% TFA). MS (ES+) m/z 465 ($M+H^+$).

Using the procedure described in Example 5 for converting Compound **5c** to Compound **5**, Compound **8b** was converted to provide Compound **8** as an HCl salt. MS (ES+) m/z 451 ($M+H^+$). ^1H NMR (DMSO-d_6, 300 MHz) δ 1.03 (m, 2H), 1.19 (m, 2H), 1.49 (m, 4H), 1.68 (m, 1H), 1.72 (m, 4H), 2.72 (m, 2H), 2.98 (m, 2H), 3.18 (m, 1H), 3.65 (m, 2H), 4.33 (m, 2H), 7.25 (m, 2H), 7.51 (m, 1H), 7.73 (m, 1H), 8.21 (m, 1H), 8.31 (s, 1H), 8.65 (m, 2H).



Using the procedure of Example 8 and the appropriate reagents and starting materials known to those skilled in the art, other compounds of the present invention may be prepared including, but not limited to:

Cpd	Name	MS (m/z)
20	β-(1,3-benzodioxol-5-yl)-1-[1-oxo-3-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)propyl]-4-piperidinepentanoic acid	494
21	6-methoxy-β-[2-[1-[1-oxo-3-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)propyl]-4-piperidinyl]ethyl]-3-pyridinepropanoic acid	481

and pharmaceutically acceptable salts thereof.

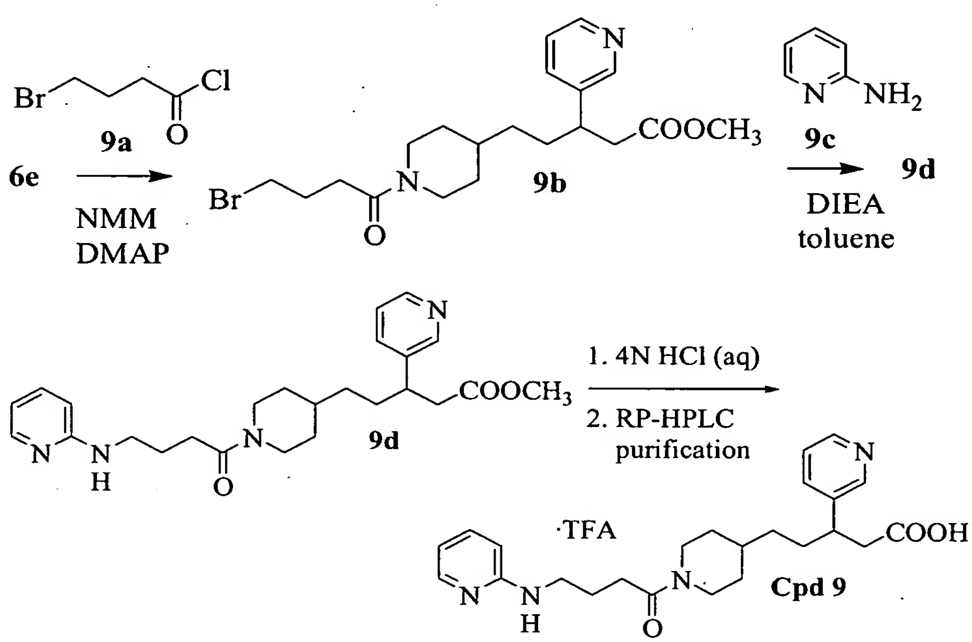
Example 9

β-[2-[1-[1-Oxo-4-(2-pyridinylamino)butyl]-4-piperidinyl]ethyl]-3-pyridinepropanoic acid (Cpd **9**)

A mixture of Compound **6e** (0.14 g, 0.44 mmol) in DCM (10 mL) and NMM (0.09 mL, 0.89 mmol) was stirred for 0.5 h at rt then cooled in an ice bath. 4-Bromobutyrylchloride Compound **9a** (0.06 mL, 0.58 mmol) and NMM (0.09 mL, 0.89 mmol) were added and the reaction mixture was stirred for 6 h at 0 °C and overnight at rt. The reaction mixture was washed with saturated NH_4Cl solution (5 mL), water (5 mL) and 1N HCl (3 x 10 mL). The organic layer was dried (Na_2SO_4) and concentrated *in vacuo* to yield Compound **9b** as a viscous oil. MS (ES+) m/z 345 (M–Br).

DIEA (0.73 mL, 4.23 mmol) was added to a stirred solution of Compound **9b** (0.60 g, 1.41 mmol) and 2-aminopyridine Compound **9c** (0.39 g, 4.23 mmol) in toluene (10 mL). The mixture was refluxed overnight and concentrated *in vacuo*. The residue was purified by RP-HPLC (2-30% acetonitrile/water, 0.1% TFA) to give Compound **9d** as an oil. MS (ES+) m/z 439 ($M+H^+$).

Using the procedure described in Example 6 for converting Compound **6h** to Compound **6**, Compound **9d** was converted to Compound **9** (purified by RP-HPLC: 2-30% acetonitrile/water, 0.1% TFA). MS (ES+) m/z 425 ($M+H^+$). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.01 (m, 2H), 1.11 (m, 4H), 1.36 (m, 1H), 1.69 (m, 4H), 2.16 (m, 2H), 2.39 (m, 2H), 3.21 (m, 2H), 3.76 (m, 2H), 4.26 (m, 2H), 4.61 (m, 1H), 7.31-8.72 (m, 8H).



Using the procedure of Example 9 and the appropriate reagents and starting materials known to those skilled in the art, other compounds of the present invention may be prepared including, but not limited to:

Cpd	Name	MS (m/z)
22	β-[2-[1-[1-oxo-4-(2-pyridinylamino)butyl]-4-piperidinyl]ethyl]-3-quinolinepropanoic acid	475

Cpd	Name	MS (m/z)
23	β-(1,3-benzodioxol-5-yl)-1-[1-oxo-4-(2-pyridinylamino)butyl]-4-piperidinepentanoic acid	468
24	β-(1,3-benzodioxol-5-yl)-1-[1-oxo-4-(2-pyridinylamino)butyl]-4-piperidinepropanoic acid	440
25	6-methoxy-β-[2-[1-[1-oxo-4-(2-pyridinylamino)butyl]-4-piperidinyl]ethyl]-3-pyridinepropanoic acid	455

and pharmaceutically acceptable salts thereof.

Example 10

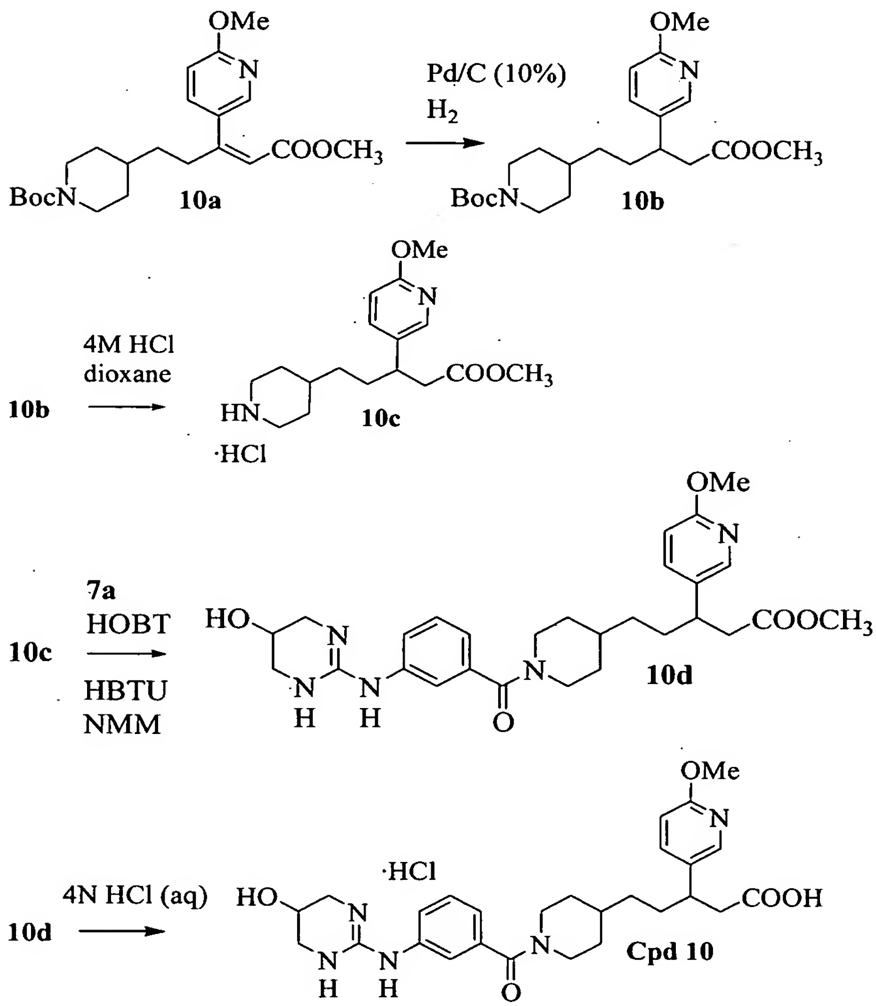
6-Methoxy-β-[2-[1-[3-[(1,4,5,6-tetrahydro-5-hydroxy-2-pyrimidinyl)amino]benzoyl]-4-piperidinyl]ethyl]-3-pyridinepropanoic acid (Cpd **10**)

Using the procedure described in Example 6 for converting Compound **6c** to Compound **6d**, Compound **10a** was converted to Compound **10b** (colorless liquid; purified by flash chromatography on silica gel, 10-15% ethyl acetate/hexane with a few drops of TEA). MS (ES+) m/z 407 ($M+H^+$) as a racemic mixture that was enantiomerically separated using a chiralcel OJ column eluting with hexane/ethanol (75:25). 1H-NMR (DMSO-d_6, 300 MHz) δ 1.04 (m, 4H), 1.19 (m, 2H), 1.47 (s, 9H), 1.61 (m, 1H), 1.73 (m, 2H), 2.66 (m, 4H), 3.02 (m, 2H), 3.61 (s, 3H), 3.92 (s, 3H), 4.01 (m, 1H), 6.81 (d, J = 7 Hz, 1H), 7.38 (d, J = 7 Hz, 1H), 8.05 (s, 1H).

Using the procedure described in Example 6 for converting Compound **6d** to Compound **6e**, Compound **10b** was converted to provide Compound **10c** as an HCl salt. MS (ES+) m/z 307 ($M+H^+$). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 0.98 (m, 2H), 1.18 (m, 1H), 1.53 (m, 4H), 1.81 (m, 2H), 2.62 (m, 2H), 2.81 (m, 4H), 3.22 (m, 1H), 3.53 (s, 3H), 3.83 (s, 3H), 6.76 (d, J = 9 Hz, 1H), 7.63 (m, 1H), 8.04 (m, 1H). Anal. Calcd for $C_{17}H_{26}N_2O_3$-1.63 CF_3COOH-0.2 H_2O: C, 49.08; H, 5.70; N, 5.65; H_2O, 0.73. Found: C, 49.10; H, 5.66; N, 5.65; H_2O, 0.93.

Using the procedure described in Example 7 for converting Compound **7a** to

Compound **7b**, Compound **7a** was reacted with Compound **10c** to produce Compound **10d**. Using the procedure described in Example 3 for converting Compound **3n** to Compound **3**, Compound **10d** was converted to produce Compound **10** as an HCl salt (purified by RP-HPLC: 5-50% acetonitrile/water, 0.1% TFA). MS (ES+) m/z 510 ($M+H^+$). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 0.99 (m, 2H), 1.14 (m, 1H), 1.53 (m, 6H), 1.67 (m, 2H), 2.58 (m, 2H), 2.94 (m, 1H), 3.15 (d, J = 11 Hz, 2H), 3.33 (d, J = 12 Hz, 2H), 3.81 (s, 3H), 3.86 (m, 2H), 4.09 (m, 1H), 6.75 (d, J = 9 Hz, 1H), 7.12-7.29 (m, 4H), 7.63 (m, 1H), 8.03 (m, 1H).



Example 11

Using the procedures described in Examples 6 and 8 for preparing Compound **8**, the

enantiomers of Compound **21** were produced from the enantiomers of **10b**.

The two pure chiral intermediates **10b-1** (isomer 1: faster eluting) and **10b-2** (isomer 2: slower eluting) were obtained by chiral HPLC chromatography (stationary phase: 500 g of Chiralcel OJ; eluent: hexane/ethanol 75/25; wavelength: 220 nm). Compounds **10b-1** and **10b-2** were converted individually to **21a** and **21b**, respectively, by the same methods used to convert **6d** to **8** in Examples 6 and 8.

Using the procedure of Example 11 and the appropriate solvents, columns, reagents and starting materials known to those skilled in the art, other compounds of the present invention may be prepared including, but not limited to:

Cpd	Name	MS (m/z)
28a	6-methoxy-β-[[1-[1-oxo-3-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)propyl]-4-piperidinyl]methyl]-3-pyridinepropanoic acid	467
28b	6-methoxy-β-[[1-[1-oxo-3-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)propyl]-4-piperidinyl]methyl]-3-pyridinepropanoic acid	467

Example 12

β-(1,3-Benzodioxol-5-yl)-1-[1-oxo-3-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)propyl]-4-piperidinebutanoic acid (Cpd **11**)

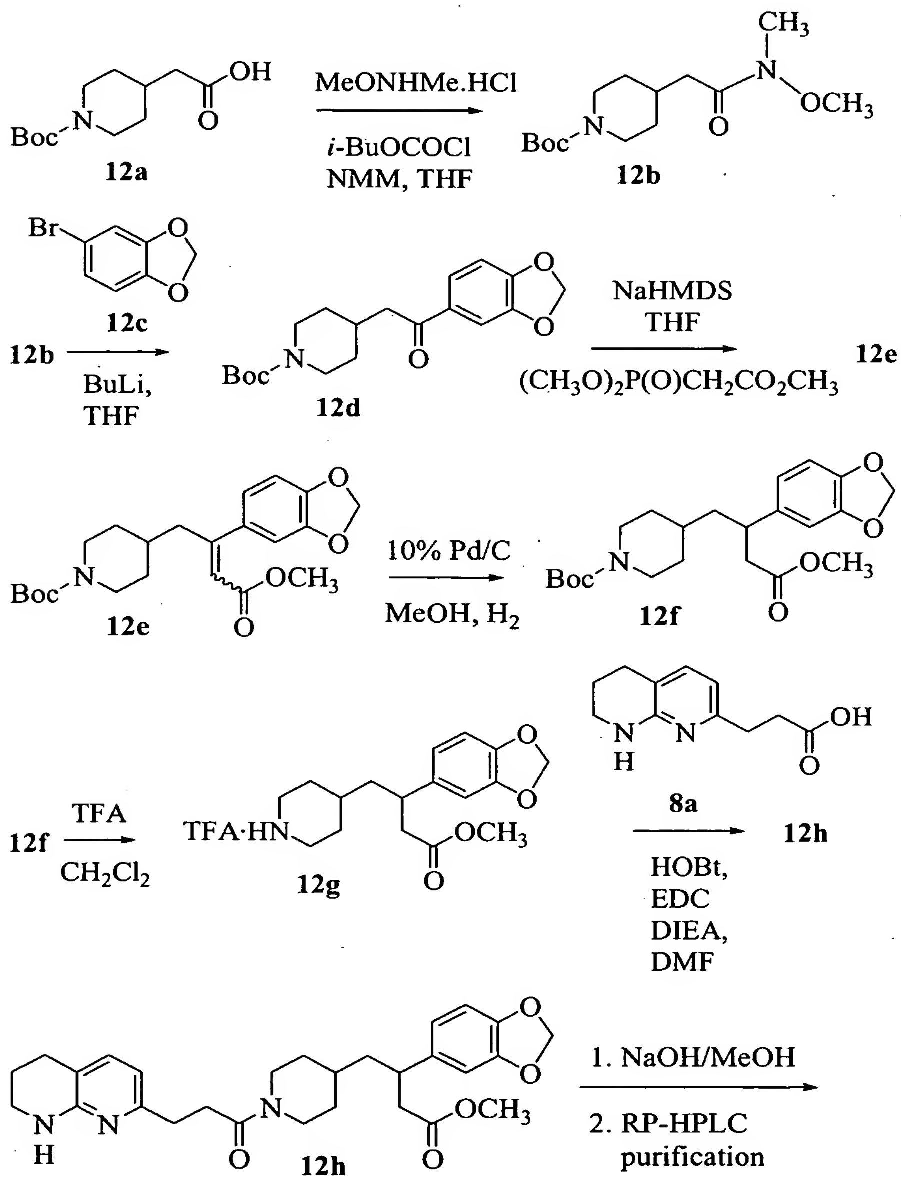
To a solution of Compound **12a** (5 g, 20.55 mmol) and NMM (4.96 mL, 45.11 mmol) in anhydrous THF (50 mL) at -20 °C under nitrogen, isobutyl chloroformate (2.67 mL, 20.58 mmol) was added *via* syringe. The mixture was stirred for 30 min and *N,O*-dimethylhydroxylamine (2 g, 20.5 mmol) was added in one portion. The mixture was warmed slowly to rt and stirred for 2 d. After concentration *in vacuo*, the residue was partitioned between EtOAc and 1N HCl. The organic phase was separated, washed with H_2O and saturated $NaHCO_3$, dried (Na_2SO_4) and concentrated *in vacuo* to afford Compound **12b** as an oil. Compound **12b** was used in the next reaction without further purification. Butyllithium (2.5M in hexane, 4.19 mL, 10.48 mmol) was added dropwise to a solution of 4-bromo-1,2-(methylenedioxy)benzene Compound **12c** (1.26

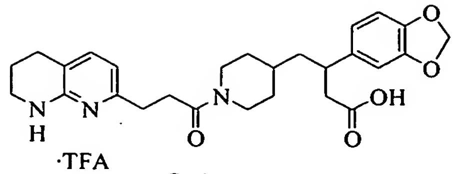
mL, 10.48 mmol) in THF (40 mL) at -78 °C. The mixture was stirred at -78 °C for 30 min and a solution of Compound **12b** (2 g, 6.98 mmol) in THF (10 mL) was added dropwise. After the mixture was stirred at -78 °C for 30 min, the cooling bath was removed. The mixture was stirred an additional 2 h at rt and quenched with a saturated NH_4Cl solution. The organic phase was separated, washed with brine, dried (Na_2SO_4) and concentrated. The residue was purified via RP-HPLC to yield Compound **12d** as an oil.

Sodium hexamethyldisilazide (1.0M in THF, 2.07 mL, 2.07 mmol) was added dropwise to a solution of trimethyl phosphonoacetate (0.33 mL, 2.07 mmol) in THF (10 mL) at 0 °C. The mixture was stirred at 0 °C for 30 min and a solution of Compound **12d** (0.18 g, 0.52 mmol) in THF (5 mL) was added dropwise. The mixture was heated to reflux for 16 h then stirred at rt for additional 24 h, cooled, diluted with Et_2O (30 mL) and washed with sat. $NaHCO_3$ and brine. The organic layer was dried (Na_2SO_4) and concentrated. The residue was purified via RP-HPLC to give Compound **12e**. A solution of Compound **12e** (0.5 g, 1.24 mmol) in MeOH (20 mL) was hydrogenated at 40 psi of H_2 in the presence of 10% palladium on carbon (0.2 g) for 16 h. The catalyst was removed by filtration over celite. The filtrate was concentrated *in vacuo* to yield Compound **12f** as an oil. Compound **12f** was used in the next reaction without further purification. TFA (5 mL) was added to a solution of Compound **12f** (0.37 g, 0.91 mmol) in DCM (20 mL). The mixture was stirred at rt for 30 min, concentrated *in vacuo* and the residue was purified via RP-HPLC to give Compound **12g** as an oil.

To a solution of Compound **8a** (0.28 g, 1.15 mmol) in DMF (40 mL), 1-HOBt (0.135 g, 1.0 mmol), EDC (0.192 g, 1.0 mmol) and DIEA (0.35 mL, 2 mmol) were added under Argon at rt. The mixture was stirred at rt for 45 min. A solution of Compound **12g** (0.28 g, 0.067 mmol) and DIEA (0.35 mL, 2 mmol) in DMF (10 mL) was added to the mixture containing Compound **8a**. The resulting mixture was stirred overnight at rt. Water (2 mL) was added, followed by DCM (20 mL). The organic layer was separated, dried (Na_2SO_4) and concentrated. The resulting crude Compound **12h** was used as such in the next reaction. The crude Compound **12h** was dissolved in MeOH (20 mL) and 3N aqueous NaOH (6 mL) was added. The mixture was stirred at rt for 5 h and

neutralized with 2N HCl. After the solvent was evaporated, the residue was purified via RP-HPLC to yield Compound **11**. MS (ES+) m/z 480 (M+H$^+$). 1H-NMR of Compound 11: ^{1}HNMR ($CDCL_3$, 300 MHz) δ 1.09 (m, 2H,), 1.30 (m, 1H), 1.4-1.7 (m, 3H), 1.86 (m, 1H), 1.94 (m, 2H), 2.47 (m, 1H), 2.58 (d, J = 7.5 Hz, 2H), 2.7-3.1 (m, 7H), 3. 15 (m, 1H), 3.51 (br s, 2H), 3.99 (dd, J = 5.3 Hz, 14.3 Hz, 2H), 4.49 (dd, J = 5.3 Hz, 14.3 Hz, 2H), 5.97 (s, 2H), 6.45 (d, J = 7.5 Hz, 1H), 6.66 (d, J = 7.8 Hz, 1H), 6.69, (s, 1H), 6.75 (d, J = 7.8 Hz, 1H), 7.33 (d, J = 7.5 Hz, 1H), 9.82 (s, 2H), 15.0 (s, 1H).





Cpd 11

Using the procedure of Example 12 and the appropriate reagents and starting materials known to those skilled in the art, other compounds of the present invention may be prepared including, but not limited to:

Cpd	Name	MS (m/z)
26	β-(1,3-benzodioxol-5-yl)-1-[1-oxo-4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl]-4-piperidinebutanoic acid	494
27	β-(1,3-benzodioxol-5-yl)-1-[3-[(1,4,5,6-tetrahydro-5-hydroxy-2-pyrimidinyl)amino]benzoyl]-4-piperidinebutanoic acid	509
28	6-methoxy-β-[[1-[1-oxo-3-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)propyl]-4-piperidinyl]methyl]-3-pyridinepropanoic acid	467
29	β-[[1-[1-oxo-4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl]-4-piperidinyl]methyl]-3-quinolinepropanoic acid	501
30	β-(3-fluorophenyl)-1-[1-oxo-3-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)propyl]-4-piperidinebutanoic acid	454
31	β-(3-fluorophenyl)-1-[1-oxo-4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl]-4-piperidinebutanoic acid	468
32	β-[[1-[1-oxo-3-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)propyl]-4-piperidinyl]methyl]-3-quinolinepropanoic acid	487
33	β-(4-fluorophenyl)-1-[1-oxo-3-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)propyl]-4-piperidinebutanoic acid	454
34	β-(4-fluorophenyl)-1-[1-oxo-4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl]-4-piperidinebutanoic acid	468
35	2-methyl-β-[[1-[1-oxo-3-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)propyl]-4-piperidinyl]methyl]-5-pyrimidinepropanoic acid	452
36	β-(2,3-dihydro-6-benzofuranyl)-1-[1-oxo-3-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)propyl]-4-piperidinebutanoic acid	478
37	β-(3,5-difluorophenyl)-1-[1-oxo-3-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)propyl]-4-piperidinebutanoic acid	472
38	β-(3,5-difluorophenyl)-1-[1-oxo-4-(5,6,7,8-tetrahydro-1,8-	486

Cpd	Name	MS (m/z)
	naphthyridin-2-yl)butyl]-4-piperidinebutanoic acid	
39	1-[1-oxo-3-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)propyl]-β-[3-(trifluoromethyl)phenyl]-4-piperidinebutanoic acid	504
40	1-[1-oxo-3-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)propyl]-β-[4-(trifluoromethoxy)phenyl]-4-piperidinebutanoic acid	520
41	β-(2-fluoro[1,1'-biphenyl]-4-yl)-1-[1-oxo-3-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)propyl]-4-piperidinebutanoic acid	530
42	β-(3-fluoro-4-methoxyphenyl)-1-[1-oxo-3-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)propyl]-4-piperidinebutanoic acid	484
43	1-[1-oxo-3-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)propyl]-β-(4-phenoxyphenyl)-4-piperidinebutanoic acid	528
44	β-[[1-[1-oxo-3-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)propyl]-4-piperidinyl]methyl]-4-isoquinolinepropanoic acid	487
45	β-[[1-[1-oxo-3-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)propyl]-4-piperidinyl]methyl]-3-pyridinepropanoic acid	437
46	β-(2,3-dihydro-5-benzofuranyl)-1-[1-oxo-3-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)propyl]-4-piperidinebutanoic acid	478
47	2,4-dimethoxy-β-[[1-[1-oxo-3-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)propyl]-4-piperidinyl]methyl]-5-pyrimidinepropanoic acid	498
48	2-methoxy-β-[[1-[1-oxo-3-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)propyl]-4-piperidinyl]methyl]-5-pyrimidinepropanoic acid	468

Example 13

β-[2-[1-[3-[(1,4,5,6-Tetrahydro-2-pyrimidinyl)amino]benzoyl]-4-piperidinyl]ethyl]-3-quinolinepropanoic acid (Cpd **12**)

A suspension of lithium aluminum hydride (3.11 g, 0.082 mol) in Et_2O (250 mL) was cooled at -55 °C under Argon. A solution of Compound **3b** (18.5 g, 0.068 mol) in Et_2O (75 mL) was added dropwise over a period of 15 min so that the temperature did not exceed -50 °C. The cooling bath was removed and the mixture was warmed up to 5 °C, cooled again to -35 °C and celite (50 g) was added. The mixture was quenched slowly with bisulphate solution (15.30 g in 43 mL of H_2O) while the temperature was kept at -30 °C. The resulting mixture was warmed to 0 °C, filtered over celite and the solid residue on the filter was washed with EtOAc (750 mL) and H_2O (500 mL). The organic

layer was separated, washed with 0.5N HCl (100 mL), saturated $NaHCO_3$ (100 mL) and brine (100 mL). The aqueous layer was extracted with EtOAc (500 mL) and the combined organic layers were dried, filtered and evaporated. The resulting residue was purified by Kugelrohr distillation (120-140 °C at 1.5-2 mm Hg) to yield Compound **13a** as a colorless oil.

A mixture of 3-bromoquinoline (10.40 g, 0.05 mol), trimethylsilylacetylene (8.48 mL, 0.06 mol), cuprous iodide (0.5 g) and *trans*-dichloro*bis*(triphenylphosphine)palladium (1 g) and TEA (15 mL) was heated at 70 °C in a sealed tube for 1 h. H_2O (150 mL) was added, followed by Et_2O (300 mL). The organic layer was separated and the aqueous layer extracted with Et_2O (200 mL). The combined organic layers were dried (Na_2SO_4) and concentrated. The residue was purified by flash column chromatography (eluent: 100% DCM) to give 3-(trimethylsilylethynyl) quinoline as a brown oil. 3-(Trimethylsilylethynyl) quinoline was dissolved in anhydrous MeOH (100 mL) and K_2CO_3 (0.69 g, 5 mmol) was added. The mixture was stirred at rt for 1 h and DCM (250 mL) was added. The mixture was filtered over celite. The filtrate was evaporated and the residue was purified by flash column chromatography to give Compound **13b** as an off-white solid.

Butyllithium (2.5M in hexane, 9.44 mL, 23.6 mmol) was added dropwise to a solution of Compound **13b** (3.62 g, 23.6 mmol) in THF (150 mL) under argon, such that the temperature did not exceed -60 °C, then the mixture was cooled to -70 °C. The mixture was stirred at -70 °C for 15 min and a solution of Compound **13a** in THF (40 mL) was added dropwise while maintaining the temperature between -60 and -70 °C. After stirring at -70 °C for 30 min, the mixture was warmed to 0 °C over a period of 20 min and H_2O (1 mL) was added. The resulting mixture was dried over K_2CO_3, filtered and evaporated. The residue was purified by flash column chromatography (eluent gradient: DCM/MeOH: 100:0 to 95:5) to yield Compound **13c** as an oil. A mixture of Compound **13c** (6.05 g) in pyridine (100 mL) was hydrogenated in the presence of Lindlar's catalyst (1 g) at 1 psi of hydrogen for 7 h. The catalyst was removed by filtration over celite and the solvent was evaporated. The residue was purified by flash column chromatography (eluent gradient: hexane/EtOAc: 9:1 to 1:1) to yield

Compound **13d** as a solid.

A solution of methyl 3-chloro-3-oxopropionate (1.24 mL, 11.53 mmol) in DCM (20 mL) was added dropwise over a period of 30 min to a solution of Compound **13d** (4.25 g, 11.53 mmol) and TEA (1.81 mL, 13 mmol) in DCM (80 mL) at 0 °C under argon. The mixture was stirred overnight at rt. Aqueous NH_4Cl solution (50 mL) and DCM (150 mL) were added. The organic layer was separated and washed with sat. $NaHCO_3$ (100 mL) and brine (100 mL), dried (Na_2SO_4), filtered and evaporated. The residue was purified by flash column chromatography (eluent gradient: hexane/EtOAc: 4:1 to 1:1) to yield Compound **13e** as an oil.

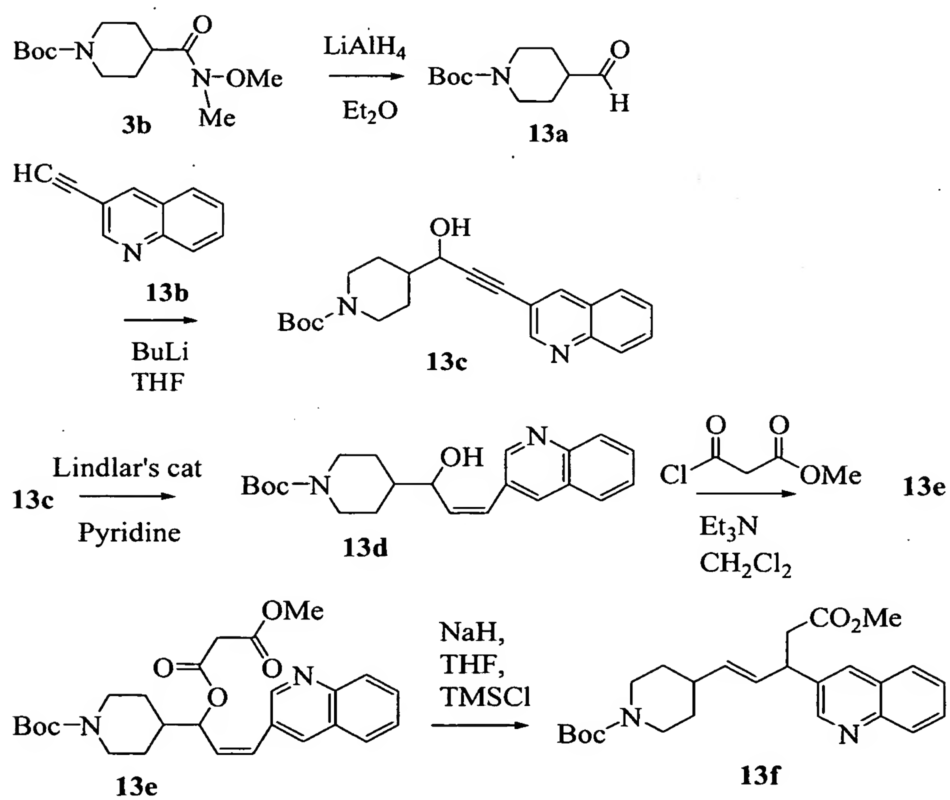
A solution of Compound **13e** (4.45 g, 9.5 mmol) in THF (20 mL) was added dropwise to a flask containing sodium hydride (60% in mineral oil, 0.57 g, 14.25 mmol, triple washed with hexane (3 x 25 mL)) at 60 °C under argon. The mixture was heated to 60 °C for 15 min. Chlorotrimethylsilane (2.41 g, 19 mmol) was added *via* syringe and the mixture was heated for 4 h at 60 °C. H_2O (0.5 mL) was added and the mixture was stirred overnight at rt. The reaction mixture was evaporated, DCM (250 mL) was added and the mixture was dried (Na_2SO_4). After filtration and evaporation, the residue was heated at 130 °C for 2 h under vacuum. Purification by flash column chromatography (eluent: 1% MeOH in DCM) gave Compound **13f** as a yellow oil.

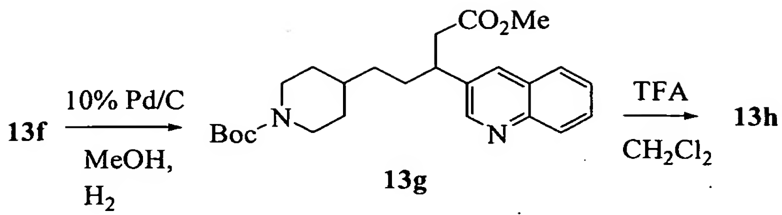
A solution of Compound **13f** (0.375 g, 0.88 mmol) in MeOH (50 mL) was hydrogenated in the presence of 10% palladium on carbon (120 mg) at 1 psi of hydrogen for 2 h. The catalyst was removed by filtration over celite and the solvent was evaporated to give a crude Compound **13g,** which was used as such for the next reaction. TFA (10 mL) was added to a solution of Compound **13g** (0.35 g, 0.82 mmol) in DCM (10 mL). The mixture was stirred at rt for 1 h and concentrated under vacuum to give crude Compound **13h,** which was used as such for the next reaction.

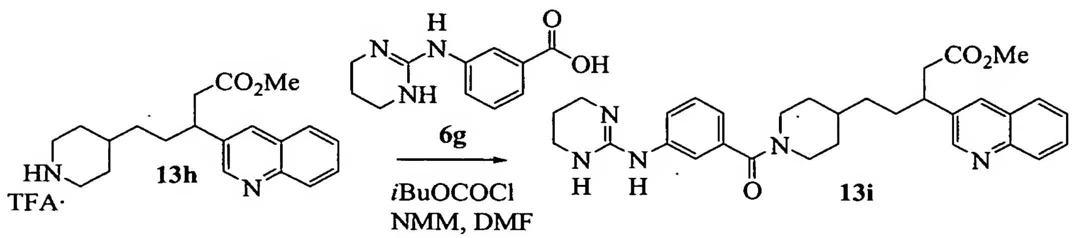
Isobutyl chloroformate (0.118 mL, 0.90 mmol) was added to a solution of Compound **6g** (230 mg, 0.90 mmol) and NMM (0.385 mL, 3.5 mmol) in DMF (8 mL) under argon at 0 °C. The mixture was stirred at 0 °C for 5 min and a solution of Compound **13h**

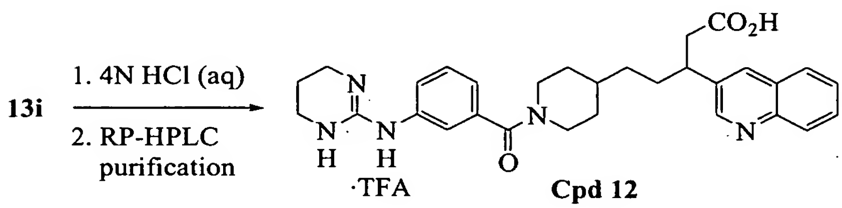
(0.455 g, 0.82 mmol) in DMF (7 mL) was added dropwise. After the addition was complete, the cooling bath was removed. The mixture was stirred at rt overnight. H_2O (0.5 mL) was added and the mixture was concentrated under high vacuum at 80 °C. The residue was purified by RP-HPLC to yield Compound **13i** as a white powder.

1N aqueous NaOH (10 mL) was added to a solution of Compound **13i** (0.15 g, 0.2 mmol) in 1,4-dioxane (10 mL). The reaction mixture was stirred for 20 h at rt and neutralized with 1N HCl (10 mL). Purification by RP-HPLC yielded Compound **12** as a white powder after lyophilization. MS (ES+) m/z 514 ($M+H^+$). 1H-NMR of Compound 12: ^{1}HNMR (DMSO-d_6, 300 MHz) δ 0.97-1.86 (m, 18H), 2.66 (m, 2H), 2.90 (m, 1H), 3.55 (m, 1H), 7.14 (s, 1H), 7. 18 (d, J = 8.5 Hz, 1H), 7. 24 (d, J = 8.5 Hz, 1H), 7.44 (t, J = 7.6 Hz, 1H), 7.65 (t, J = 7.6 Hz, 1H), 7.78 (t, J = 7.6 Hz, 1H), 8.01 (t, J = 8.5 Hz, 2H), 8.19 (s, 1H), 8.35 (s, 1H), 8.91 (s, 1H).









Using the procedure of Example 13 and the appropriate reagents and starting materials known to those skilled in the art, other compounds of the present invention may be prepared including, but not limited to:

Cpd	Name	MS (m/z)
49	β-[2-[1-[3-[(1,4,5,6-tetrahydro-5-hydroxy-2-pyrimidinyl)amino]benzoyl]-4-piperidinyl]ethyl]-3-quinolinepropanoic acid	530
50	β-[2-[1-[3-[(3,4,5,6-tetrahydro-2-pyridinyl)amino]benzoyl]-4-piperidinyl]ethyl]-3-quinolinepropanoic acid	513
51	β-[2-[1-[1-oxo-3-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)propyl]-4-piperidinyl]ethyl]-3-quinolinepropanoic acid	501
52	β-[2-[1-[1-oxo-3-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)propyl]-4-piperidinyl]ethyl]-3-quinolinepropanoic acid	507
53	β-(1,3-benzodioxol-5-yl)-1-[3-[(3,4,5,6-tetrahydro-2-pyridinyl)amino]benzoyl]-4-piperidinepentanoic acid	506
54	β-(1,3-benzodioxol-5-yl)-1-[3-[(1,4,5,6-tetrahydro-5-hydroxy-2-pyrimidinyl)amino]benzoyl]-4-piperidinepentanoic acid	523
55	β-(1,3-benzodioxol-5-yl)-1-[(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)acetyl]-4-piperidinepentanoic acid	480

Example 14

1-[1-oxo-3-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)propyl]-β-phenyl-4-piperidinebutanoic acid (Cpd **13**)

Di-*tert*-butyl dicarbonate (41.25g, 189 mmol) was added in one portion to a solution of 4-(2-hydroxyethyl)piperidine Compound **14a** (24.42g, 189 mmol) in DMF (200 mL) at 0 °C. After 1 hour, the cooling bath was removed and the reaction mixture was allowed to stir for 20 h at RT. The reaction mixture was treated with Et_2O (200 mL) and H_2O (500 mL). The organic layer was separated, washed with sat NH_4Cl (200 mL) and brine (200 mL) and dried $MgSO_4$). After filtration and evaporation, Compound **14b** was obtained as a transparent oil and used as such without further purification.

A solution of DMSO (14g, 179 mmol) in DCM (80 mL) was added dropwise over a period of 1.5 h to a 2M solution of oxalyl chloride (62.8mL, 125.6 mmol) in dry DCM (200 mL) at -78 °C, such that the temperature did not exceed -60 °C. A solution of Compound **14a** in DCM (30 mL) was added dropwise at -78°C over a 50 min period. After stirring 30 min at -78 °C, the cooling bath was removed and the temperature of the reaction mixture was allowed to rise to -30 °C over a 30 min period. TEA (25.41 g, 251 mmol) was added and the reaction mixture was allowed to stir for 1h at rt. The solid precipitate that had formed was removed by filtration and the filtrate was washed with 0.3N HCl (2 x 100 mL) and brine (200 mL). The organic phase was dried (Na_2SO_4), evaporated and the residue was purified via flash column chromatography (eluent gradient: hexane/EtOAc 100/0 to 70/30) to yield Compound **14c**.

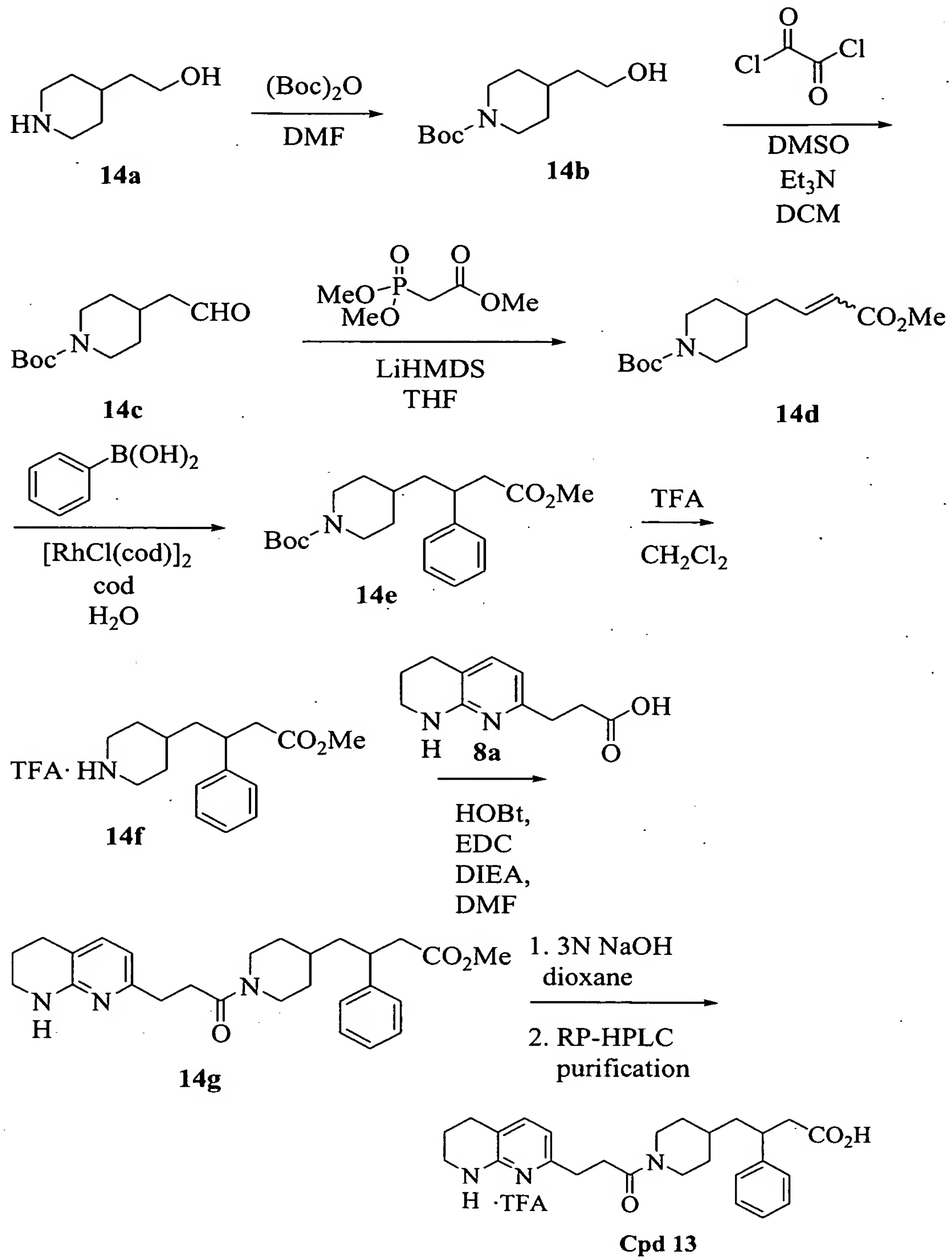
A 1M solution of LiHMDS (73 mL, 73 mmol) was added via syringe to a solution of trimethyl phosphonoacetate (13.29g, 73 mmol) in THF (200 mL) at -78°C under argon. The reaction mixture was then stirred for 20 min at -78°C and a solution of Compound **14c** (8.3g, 36.5 mmol) in THF (50 mL) was added over a 30 min period. After stirring for 15 min at -78 °C, the cooling bath was removed and the reaction mixture was heated to reflux for 2. The reaction mixture was allowed to cool to room temperature and a saturated NH_4Cl solution (40 mL) was added. Et_2O (200 mL) was added, the organic layer was separated and washed with brine (140 mL) and dried (Na_2SO_4). After

filtration and evaporation, the residue was purified via flash column chromatography (eluent gradient: hexane/EtOAc: 100/0 to 85/15), yielding a mixture of *E*- and *Z*-isomers of Compound **14d**.

Compound **14d**, phenyl boronic acid (1.55g, 12.32 mmol), [RhCl(Cod)]2 (0.1g, 0.227 mmol) and Cod (0.557g, 5.15 mmol) were combined in H_2O (15mL) and heated to 100 °C for 3 h under a nitrogen atmosphere. Phenylboronic acid (1.0g, 8.2 mmol) was added again and the reaction mixture was heated to 100 °C for another 6 h. The reaction mixture was allowed to cool to rt, Et_2O (100 mL) was added and the organic layer was separated. The aqueous layer was washed with Et_2O (2 x 100 mL) and the combined organic layers were dried (Na_2SO_4), filtered and evaporated. The residue was purified via flash column chromatography, yielding Compound **14e**.

TFA (6 mL) was added to a solution of Compound **14e** (1.48 g, 4.09 mmol) in DCM (14 mL). The mixture was stirred at rt for 20 min, concentrated under vacuum and purified via RP-HPLC to yield Compound **14f** as a trifluoroacetate salt.

HOBt (0.333 g, 2.46 mmol), EDC (0.47 g, 2.46 mmol) and NMM (0.68 g, 5.28 mmol) were added to a solution of Compound **8a** (0.64 g, 2.64 mmol) in DMF (30 mL) under argon. The mixture was stirred at rt for 1 h, then a solution of Compound **14f** (0.66 g, 1.76 mmol) and NMM (0.68 g, 5.28 mmol) in DMF (10 mL) was added. The resulting mixture was stirred overnight at rt. Water (2 mL) was added, followed by DCM (20 mL). The organic layer was separated, dried (Na_2SO_4) and concentrated. The resulting crude Compound **14g** was used as such in the next reaction. To a solution of Compound **14g** in dioxane (2 mL) and H_2O (1 mL) was added NaOH (0.78g, 19.5 mmol). The mixture was stirred at rt for 5 h and neutralized with 2N HCl. After the solvent was evaporated, the residue was purified by RP-HPLC to give Compound **13** after lyophilization.



Using the procedure of Example 14 and the appropriate reagents and starting materials known to those skilled in the art, other compounds of the present invention may be prepared including, but not limited to:

Cpd	Name	MS (m/z)
56	β-(2-naphthalenyl)-1-[1-oxo-3-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)propyl]-4-piperidinebutanoic acid	486

and pharmaceutically acceptable salts thereof.

Example 15

Isomers 1, 2, 3, and 4 of 1,2,3,4-tetrahydro-β-[[1-[1-oxo-3-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)propyl]-4-piperidinyl]methyl]-3-quinolinepropanoic acid (Cpd **19-1**, **19-2**, **19-3**, **19-4**)

To a stirred solution of the Weinreb amide **12b** (3.00 g, 10.48 mmol) and 3-bromoquinoline Compound **15a** (10.9 g, 52.38 mmol) in THF (120 mL) were added dropwise *n*-BuLi (2.5 M solution in hexane; 21.0 mL, 52.38 mmol) over a period of 20 min at –78°C. The reaction mixture was kept below –74 °C during the addition. After the addition, the mixture was stirred for 30 min at –78 °C, and then the cooling bath was removed. The reaction mixture was allowed to warm up to rt over a period of 1 h. The reaction mixture was quenched by the addition of saturated NH_4Cl in water (50 mL), and it was extracted with EtOAc (100 mL). The organic layer was washed with brine (10 mL), and dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (30% EtOAc/hexane) to give the ketone Compound **15b** as an amber foam. MS (ES+) m/z 355.4 (M+H$^+$). ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.26 (m, 2H), 1.46 (s, 9H), 1.78 (m, 2H), 2.22 (m, 1H), 2.77 (m, 2H), 3.02 (d, J = 7 Hz, 2H), 4.08-4.18 (m, 2H), 7.64 (t, J = 7 Hz, 1H), 7.85 (t, J = 8 Hz, 1H), 7.96 (d, J = 8 Hz, 1H), 8.17 (d, J = 8 Hz, 1H), 8.70 (br s, 1H), 9.42 (br s, 1H).

To a THF (166 mL) solution of trimethyl phosphonoacetate (11.65 mL, 80.58 mmol) was added dropwise NaHMDS (1.0M in THF; 67.2 mL, 67.15 mmol) over a period of 10 min at –78 °C. The resulting partially solidified mixture was stirred at –50°C for 20 min. To the resulting thick solidified mixture, a THF (119 mL) solution of the ketone Compound **15b** (4.76 g, 13.43 mmol) was added at –50 °C over a period of 5 min.

After the addition, the cooling bath was changed to a water bath and it was stirred for 15 min. The reaction mixture was then refluxed for 2.5 h. The reaction was monitored by HPLC. After cooling to rt, the mixture was diluted with EtOAc (400 mL) and it was washed with saturated $NaHCO_3$ (50 mL×2), and brine (50 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (100 g, 6.5×5 cm, 20% to 30% EtOAc/hexane) to give the olefin Compound **15c** as an amber-red syrup, mixture of E,Z-isomers. MS (ES+) m/z 411.3 ($M+H^+$).

A MeOH (150 mL) solution of the olefin Compound **15c** (2.76 g, 6.72 mmol) was added to 10% Pd/C (5.52 g as is, 50% water wet). The solution was vacuum/N_2 degassed and then pressurized to 60 psi H_2 pressure. The reaction was agitated at rt for 22 h. The reaction mixture was filtered and the filtrates were concentrated under reduced pressure. The residue was purified by flash column chromatography (70 g, 3×25 cm column, eluting with 30% EtOAc/hexane) to afford the hydroquinoline Compound **15d** as a light yellow gum) and Compound **15e** as a minor product.

Alternatively, toluene can be used as the solvent. A solution of Compound **15c** (17.14 g, mmol), was combined with 10% Pd/C (8.6 g) in toluene (210 mL) with TEA (2.1 mL). The reaction mixture was shaken on a Parr apparatus at 50 °C and 50 psi for about 28 h. It was stopped when the hydrogen uptake slowed. After chromatography Compound **15d** was isolated. MS (ES+) m/z 417.1 ($M+H^+$). ^{1}HNMR ($CDCl_3$, 300 MHz) δ 1.0-1.6 (m, 6H), 1.45 (s, 9H), 2.0-2.7 (m, 8H), 3.00 (m, 1H), 3.26 (m, 1H), 3.67 (s, 3H), 3.83 (m, 1H), 4.11 (m, 2H), 6.49 (d, J = 8Hz, 1H), 6.62 (t, J = 7Hz, 1H), 6.97 (m, 2H).

The individual enantiomers of Compound **19** were prepared by separating the isomers of **15d** and taking them to final product Compounds **19-1**, **19-2**, **19-3**, and **19-4**, by the same method that Compound **5a** was converted to Compound **5** in Example 5, but using the tetrahydronaphthyridine Compound **8a** instead of **4a**.

The four isomers of Compound **15d** were separated by sequential chiral

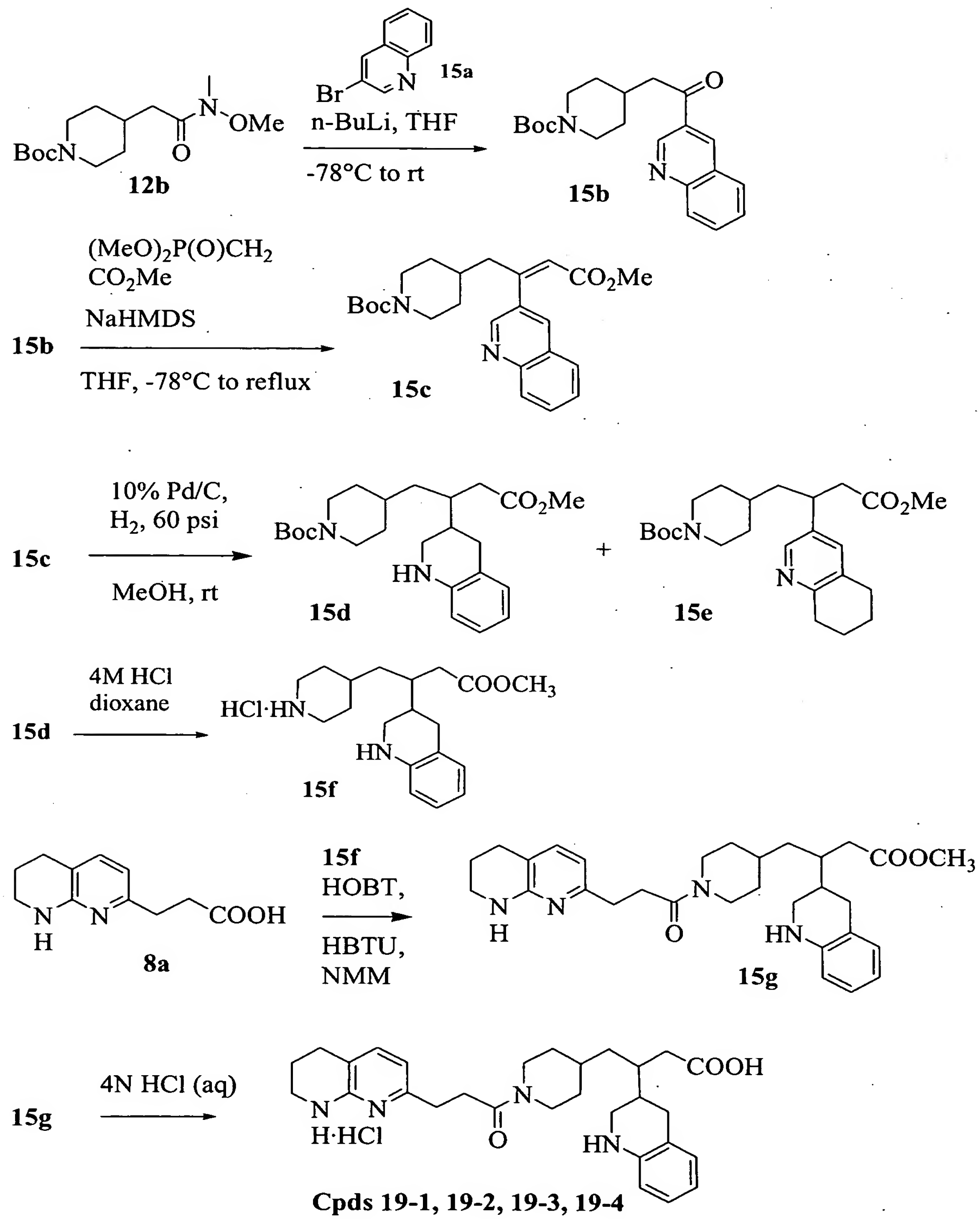
chromatography. The UV triggered preparative HPLC work was accomplished using a Dynamic Axial Compression type Prochrom LC50 column, which was filled with 500 grams of stationary phase. A Prep LC 4000 (Waters) quaternary gradient low pressure mixing pump, a K-2500 UV detector (KNAUER), a 233 XL auto injector (Gilson), a 402 Syringe pump (Gilson), a 202 fraction collector (Gilson), an rh.7030L fraction collector valve (Gilson), and Unipoint control software (Gilson) were utilized. Isomers (numbered based on elution order: isomer 1 first eluting) **15d-1** and **15d-2** were separated from isomers **15d-3** and **15d-4** using a Chiralpak® OD column: Cellulose tris-(3,5-dimethylphenylcarbamate) coated on a 20 μm silica-gel, 5 cm ID; 41 cm length ; using methanol as eluent: 100 vol% at 80 mL/min. and a wavelength 220 nM. This resulted in **15d-1** and **15d-2** as a mixture and **15d-3** and **15d-4** as a mixture. The isomers **15d-1** and **15d-2** were separated on a chiral column: Chiralpak® AD: Amylose tris-(3,5-dimethylphenylcarbamate) coated on a 20 μm silica-gel, 5 cm ID, 41 cm length; using ethanol as eluent: 100 vol% at 80 mL/min.; wavelength 220 nM. This results in two pure isomers **15d-1** and **15d-2**, which were individually converted to **19-1** and **19-2**, respectively, by the methods described in Example 5 with the appropriate reagents and starting materials.

The isomers **15d-3** and **15d-4** were separated on a chiral column: Chiralpak® AD, Amylose tris-(3,5-dimethylphenylcarbamate) coated on a 20 μm silica-gel, 500 gr; 5 cm ID; 41 cm length and as eluent using ethanol: 100 vol% at 80 mL/min.; wavelength 220 nM. This resulted in two pure isomers **15d-3** and **15d-4**, which were individually converted to **19-3** and **19-4**, respectively, by the methods described in Example 5 with the appropriate reagents and starting materials.

Cpds 19-1, 19-2, 19-3, 19-4: ^{1}H-NMR (DMSO-d_6, 300 MHz) δ 0.86-2.95 (m, 24H), 3.22 (br d, 1H), 3.41 (br s, 2H), 3.82 (br d, 1H), 4.37 (br d, 1H), 6.65 (m, 3H), 6.95 (m, 2H), 7.61 (d, J = 7 Hz, 1H), 7.95 (br s, 1H).

Compound No.	Optical Rotation of **15d** (in MeOH)	Compound No.	Optical Rotation of **19** (in MeOH)
15d-1	+30°	**19-1**	+15.85°

15d-2	+62.03°	**19-2**	+24.15°
15d-3	-64.57°	**19-3**	-24.78°
15d-4	-30.99°	**19-4**	-14.57°



Using the procedures of Example 19 and the appropriate solvents and starting materials known to those skilled in the art, other individual isomers of the compounds of the present invention may be prepared including, but not limited to:

Cpd	Name	MS (m/z)
5-1, 5-2, 5-3, 5-4	1,2,3,4-Tetrahydro-β-[1-[1-oxo-4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl]-4-piperidinyl]-3-quinolinepropanoic acid	491
58a	5,6,7,8-Tetrahydro-β-[1-[1-oxo-4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl]-4-piperidinyl]-3-quinolinepropanoic acid	491
58b	5,6,7,8-Tetrahydro-β-[1-[1-oxo-4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butyl]-4-piperidinyl]-3-quinolinepropanoic acid	491

and pharmaceutically acceptable salts thereof.

Compound No.	Optical Rotation of **5a** (in MeOH)	Compound No.	Optical Rotation of **5** (in MeOH)
5a-3	-62°	**5-3**	-26.41°
5a-4	-46°	**5-4**	-19.57°

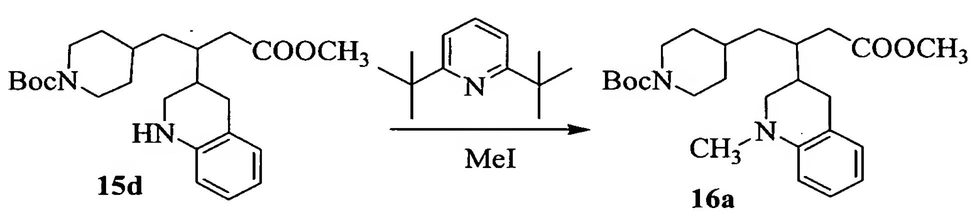
Example 16

N-Methyl-1,2,3,4-tetrahydro-β-[[1-[1-oxo-3-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)propyl]-4-piperidinyl]methyl]-3-quinolinepropanoic acid (Cpd **67**)

Compound **67** was prepared by the same method used to convert Compound **15d** to Compound **19** as described in Example 15, except in this case the intermediate

Compound **15d** was alkylated prior to the Boc deprotection step. The alkylated product Compound **16a** was converted to Compound **67** in the same manner Compound **15d** was converted to Compound **19**. Compound **15d** (280 mg, 0.67 mmol) was dissolved in anhydrous DMF (10 mL) and treated with 2,6-di-*tert*-butylpyridine (0.181 mL, 0.81 mmol) and iodomethane (0.050 mL, 0.81 mmol) and left at rt for 20 h. The crude reaction mixture was evaporated and then purified by flash chromatography (20% EtOAc in hexane, few drops of triethyl amine) to yield **16a** (90 mg, 31%) as a glassy solid. MS (ES+) m/z 431 ($M+H^+$). ^1H NMR (DMSO-d_6, 300 MHz) δ 1.0-1.7 (m, 7H), 1.45 (s, 9H), 2.0-2.7 (m, 8H), 2.88 (s, 3H), 3.01 (m, 1H), 3.09 (m, 1H), 3.67 (s, 3H), 4.01 (m, 2H), 6.4-6.6 (m, 2H), 6.96 (d, J = 7 Hz, 1H), 7.08 (t, J = 8 Hz, 1H).

Cpd	Name	MS (m/z)
67	*N*-Methyl-1,2,3,4-tetrahydro-β-[[1-[1-oxo-3-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)propyl]-4-piperidinyl]methyl]-3-quinolinepropanoic acid	505



Example 17

4-[1-(3-5,6,7,8-Tetrahydro-[1,8]naphthyridin-2-yl-propionyl)-piperidin-4-yl]-butyric acid *tert*-butyl ester (Cpd **70**)

Using the procedure described in Example 3 for converting Compound **3d** to Compound **3e**, Compound **14d** was converted to Compound **17a**. MS (ES+) m/z 286 ($M+H^+$).

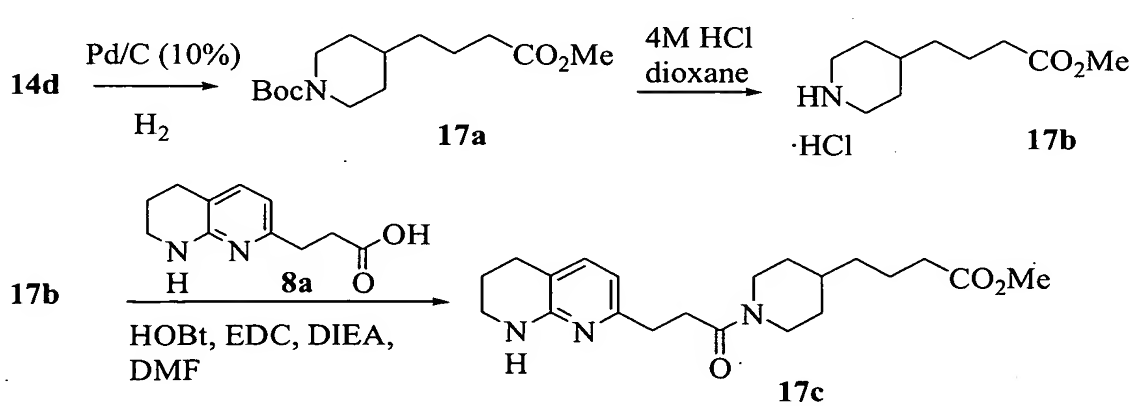
Using the procedure described in Example 3 for converting Compound **3e** to

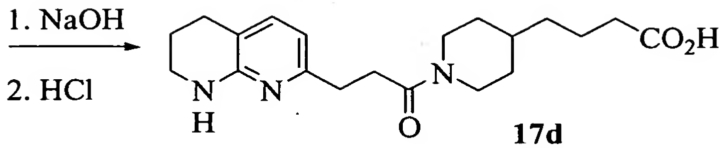
Compound **3f**, Compound **17a** was converted to Compound **17b**. MS (ES+) m/z 186 (M+H$^+$).

Using the procedure described in Example 14 for converting Compound **14f** to Compound **14g**, Compound **17b** was reacted with Compound **8a** to yield Compound **17c**. MS (ES+) m/z 374.2 (M+H$^+$).

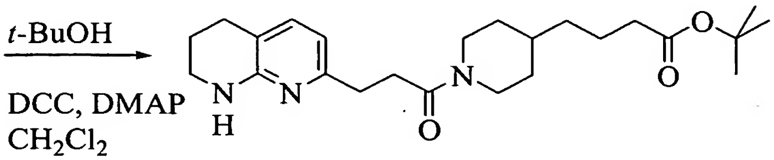
3N NaOH (3.21 mL, 9.63 mmol) was added to a solution of Compound **17c** (1.8g, 4.82 mmol) in MeOH (9 mL). The resulting mixture was stirred for 4.5 h at rt. 2N HCl (4.82 mL, 9.64 mmol) was added, and the mixture was concentrated under reduced pressure. DCM was added to the residue, and the solid was removed via filtration. The filtrate was evaporated to yield Compound **17d**. MS (ES+) m/z 360.3 (M+H$^+$).

t-Butanol (0.476 mL, 4.98 mmol), 1,3-dicyclohexylcarbodiimide (1M in DCM; 1 mL, 1 mmol), and DMAP (1M in DCM; 0.11 mL, 0.11 mmol) were added to a solution of Compound **17d** (0.3g, 0.83 mmol) in DCM (2 mL). The resulting mixture was stirred overnight at rt. The mixture was filtered and concentrated at reduced pressure and the residue was purified by RP-HPLC (10-90% MeCN/water, 0.1% TFA) to yield C Compound **70**. MS (ES+) m/z 388.4 (M+H$^+$). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.98-1.86 (m, 9H), 1.42 (s, 9H), 1.93 (m, 2H), 2.20 (t, J = 7.5 Hz, 2H), 2.58 (t, J = 7.5 Hz, 1H), 2.68-3.10 (m, 7H), 3.50 (t, J = 5.4 Hz, 2H), 4.05 (d, J = 12.3 Hz, 1H), 4.54 (d, J = 12.3 Hz, 1H), 6.49 (d, J = 6.9 Hz, 1H), 7.33 (d, J = 6.9 Hz, 1H).



17c


17d

17d


Cpd 70

Using the procedure of Example 17 and the appropriate reagents and starting materials known to those skilled in the art, other compounds of the present invention may be prepared including, but not limited to:

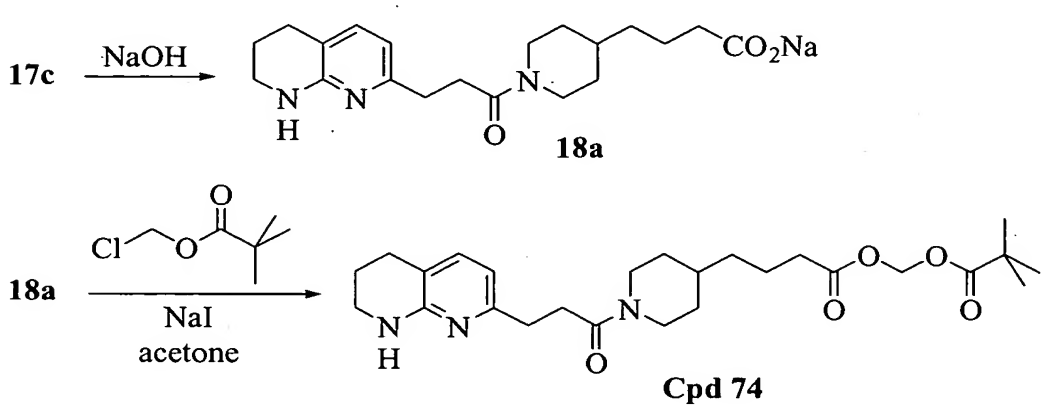
Cpd	Name	MS (m/z)
68	4-[1-(3-5,6,7,8-Tetrahydro-[1,8]naphthyridin-2-yl-propionyl)-piperidin-4-yl]-butyric acid ethyl ester	388.4
69	4-[1-(3-5,6,7,8-Tetrahydro-[1,8]naphthyridin-2-yl-propionyl)-piperidin-4-yl]-butyric acid isopropyl ester	402.3
71	4-[1-(3-5,6,7,8-Tetrahydro-[1,8]naphthyridin-2-yl-propionyl)-piperidin-4-yl]-butyric acid octyl ester	472.5
72	4-[1-(3-5,6,7,8-Tetrahydro-[1,8]naphthyridin-2-yl-propionyl)-piperidin-4-yl]-butyric acid isobutyl ester	416.4
73	4-[1-(3-5,6,7,8-Tetrahydro-[1,8]naphthyridin-2-yl-propionyl)-piperidin-4-yl]-butyric acid methyl ester	374.2

Example 18

4-[1-(3-5,6,7,8-Tetrahydro-[1,8]naphthyridin-2-yl-propionyl)-piperidin-4-yl]-butyric acid 2,2-dimethyl-propionyloxymethyl ester (Cpd **74**)

3N NaOH (3.21 mL, 9.63 mmol) was added to a solution of Compound **17c** (1.8g, 4.82 mmol) in MeOH (10 mL). The resulting mixture was stirred for 4 h at rt and concentrated at reduced pressure to yield **18a**. MS (ES+) m/z 360.3 (M+H$^+$).

Chloromethyl pivalate (0.21 mL, 1.46 mmol) and 25% aqueous NaI (0.13 mL) were added to a suspension of Compound **18a** (0.5g, 1.3 mmol) in acetone (10 mL) and the resulting mixture was heated to reflux for 5 h. The solvent was removed at reduced pressure and the residue was purified by RP-HPLC (10-90% MeCN/water, 0.1% TFA) to yield Compound **74**. MS (ES+) m/z 474.3 (M+H$^+$). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.05 (m, 2H), 1.20 (s, 9H), 1.27 (m, 2H), 1.50 (m, 1H), 1.67 (m, 2H), 1.77 (m, 2H), 1.95 (m, 2H), 2.37 (t, J = 7.8 Hz, 2H), 2.57 (t, J = 13.2 Hz, 1H), 2.75 (t, J = 7.5 Hz, 2H), 2.82 (m, 2H), 2.95-3.10 (m, 3H), 3.51 (t, J = 6 Hz, 2H), 4.05 (d, J = 13.2 Hz, 1H), 4.56 (d, J = 13.2 Hz, 1H), 5.76 (s, 2H), 6.50 (d, J = 7.5 Hz, 1H), 7.33 (d, J = 7.5 Hz, 1H).



Example 19

3-(2,3-Dihydro-benzofuran-6-yl)-4-[1-(3-5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl-propionyl)-piperidin-4-yl]-butyric acid (Cpd **36a**)

Using the procedure described in Example 12 for converting Compound **12b** to Compound **12d**, Compound **12b** was converted to Compound **19b** upon reaction with *n*-BuLi and 6-bromo-2,3-dihydrobenzofuran **19a** (Compound **19a** was obtained in three steps from 1,4-dibromo-2-fluorobenzene as described in Organic Letters (2001), 3(21), 3357-3360). MS (ES+) m/z 368.4 (M+Na$^+$).

Using the procedure described in Example 12 for converting Compound **12d** to Compound **12e**, Compound **19b** was converted to Compound **19c**. MS (ES+) m/z 424.4 ($M+Na^+$).

Using the procedure described in Example 12 for converting Compound **12e** to Compound **12f**, Compound **19c** was converted to Compound **19d**. MS (ES+) m/z 426.5 ($M+Na^+$).

Racemic Compound **19d** was separated into the two enantiomerically pure Compounds **19e** and **19f** on a chiral column using methanol as eluent (Stationary phase: Chiralpak AD 20 μm (Daicel); eluent: methanol; column diameter: 50 mm; detector: 0.5 mm Knauer superpreparative cell; wavelength: 225 nm). Compound **19f** (second eluting isomer): $[\alpha]^{20}_{D}$ –24.3 (*c* 0.717, MeOH). Compound **19e** (first eluting isomer): $[\alpha]^{20}_{D}$ +24.8 (*c* 0.775, MeOH).

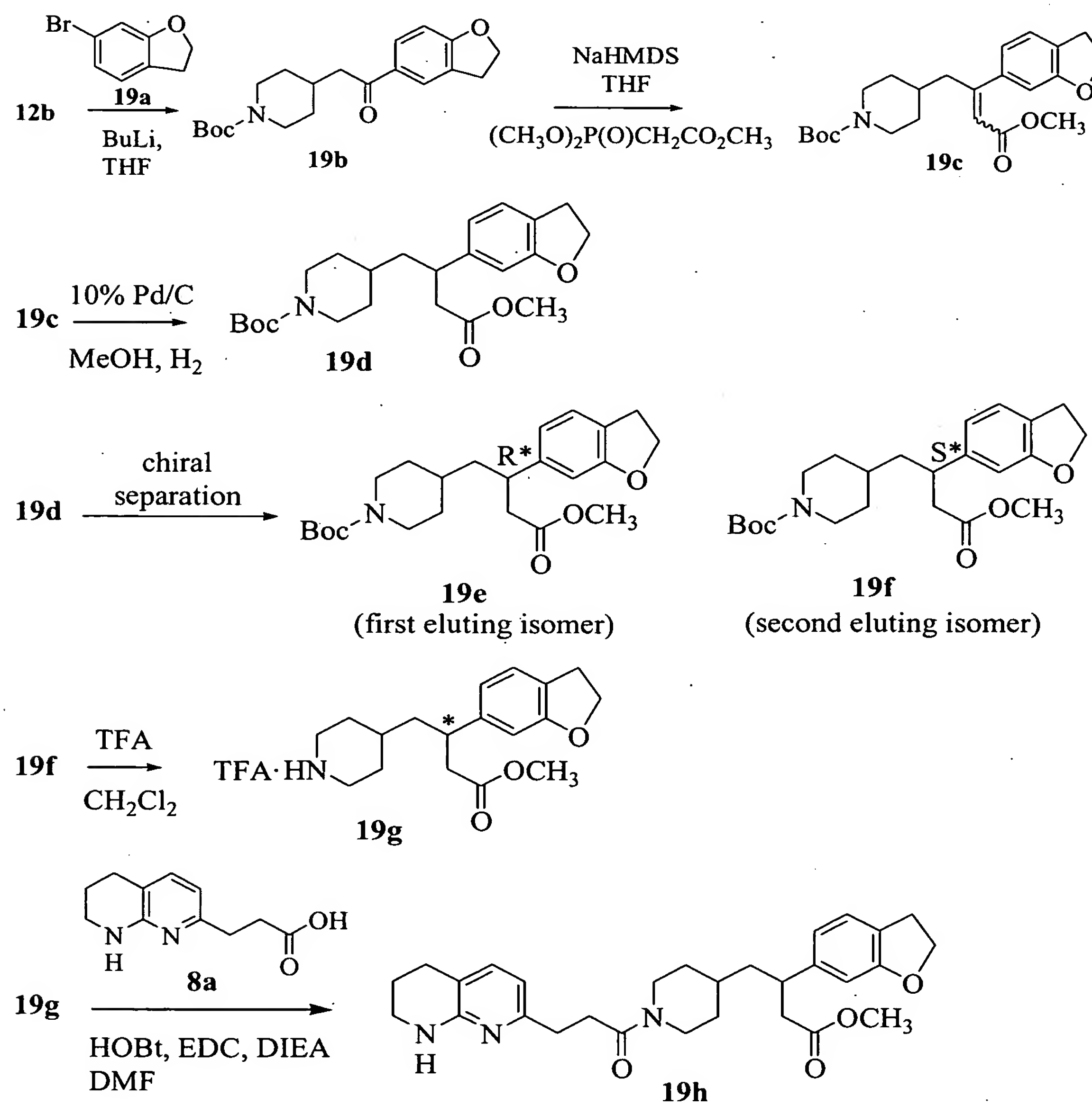
Using the procedure described in Example 12 for converting Compound **12f** to Compound **12g**, Compound **19f** was converted to Compound **19g**. MS (ES+) m/z 304.4 ($M+H^+$).

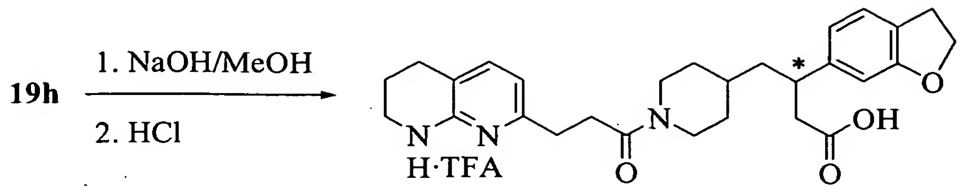
Using the procedure described in Example 12 for converting Compound **12g** to Compound **12h**, Compound **19g** was converted to Compound **19h**. MS (ES+) m/z 492 ($M+H^+$).

The crude Compound **19h** was dissolved in MeOH (20 mL) and 3N aqueous NaOH (6 mL) was added. The mixture was stirred at rt for 5 h and neutralized with 2N HCl. After the solvent was evaporated, the residue was purified via RP-HPLC to yield Compound **36a**. MS (ES+) m/z 478.8 ($M+H^+$). ^{1}HNMR ($CDCl_3$, 300 MHz) δ 1.09 (1.07 (m, 2H), 1.27 (m, 1H), 1.40-1.86 (m, 3H), 1.73-2.0 (m, 3H), 2.42 (t, J = 12.5 Hz, J = 4.4 Hz, 1H), 2.55 (d, J = 7.3 Hz, 2H), 2.67-3.24 (m, 10H), 3.5 (br s, 2H), 3.93 (dd, J = 19.8 Hz, J = 16.2 Hz, 1H), 4.43 (dd, J = 16.2 Hz, J = 14.7 Hz, 1H),, 4.57 (t, J = 7.5 Hz, 1H), 6.62 (s, 1H), 6.67 (d, J = 8.1 Hz, 1H), 7.10 (d, J = 8.1 Hz, 1H), 7.33 (d, J = 7.5 Hz, 1H), 8.41 (br s, 1H). Anal. Calcd for $C_{28}H_{35}N_3O_4$-1.05 HCl-0.6 H_2O: C, 63.86; H,

7.13; N, 7.98; Cl, 7.07; H_2O, 2.06. Found: C, 63.67; H, 7.32; N, 8.12; Cl, 6.94; H_2O, 1.91. $[\alpha]^{20}_D$ −31.1 (*c* 0.675, MeOH).

Enantiomer **36b** was obtained from the fast moving enantiomer Compound **19e** using procedures described for converting **19f** to Compound **36a**.





Cpd 36a

Example 20

3-(4-Hydroxy-3-methoxy-phenyl)-4-[1-(3-5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl-propionyl)-piperidin-4-yl]-butyric acid (Cpd **76**)

To a solution of bromo-methoxyphenol Compound **20a** (10g, 49.2 mmol) and *N,N*-diethyl-*N*-diisopropylamine (0.7g, 54.2 mmol) in dry DCM (100 mL) was added 2-(trimethylsilyl)ethoxymethyl chloride (9.03g, 54.2 mmol). The resulting mixture was stirred for 2 h at rt, and water and brine were added. The organic layer was separated and dried over Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified via flash column chromatography (silica gel; eluent:hexane:EtOAc; 9:1) to yield Compound **20b**. MS (ES+) m/z 396/398 ($M+H^+$).

Using the procedure described in Example 12 for converting Compound **12b** to Compound **12d**, Compound **12b** was converted to Compound **20c**. MS (ES+) m/z 502.2 ($M+Na^+$).

Using the procedure described in Example 12 for converting Compound **12d** to Compound **12e**, Compound **20c** was converted to Compound **20d**. MS (ES+) m/z 558.2 ($M+Na^+$).

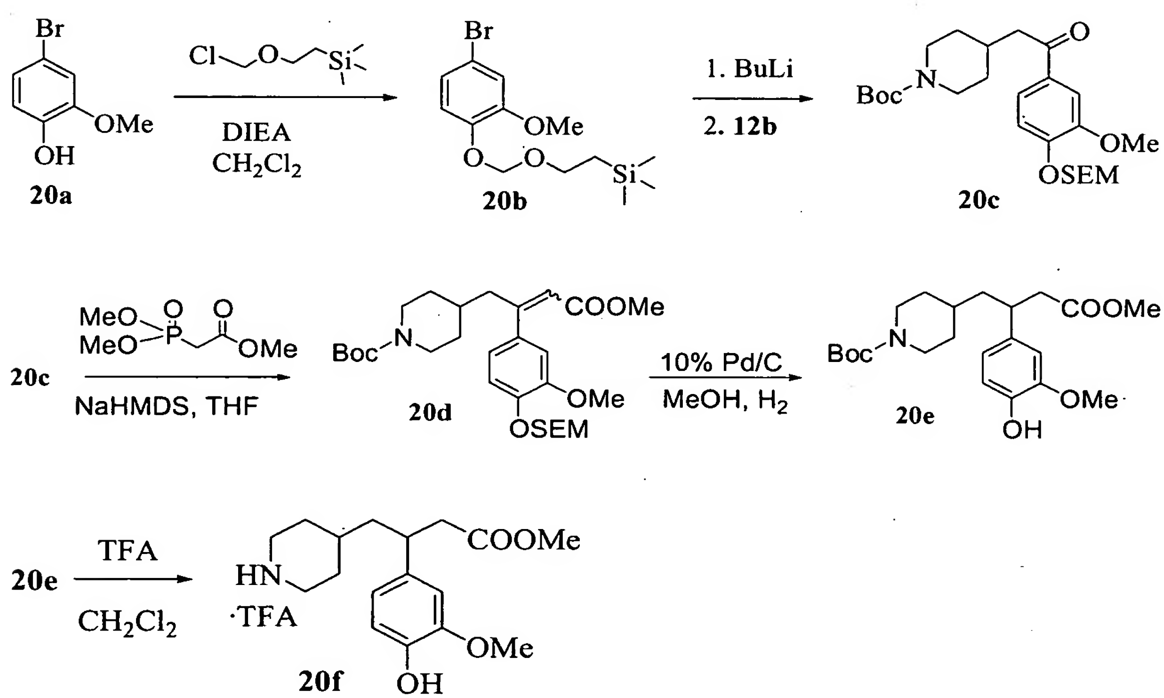
Using the procedure described in Example 12 for converting Compound **12e** to Compound **12f**, Compound **20d** was converted to Compound **20e**. MS (ES+) m/z 408.3 ($M+H^+$).

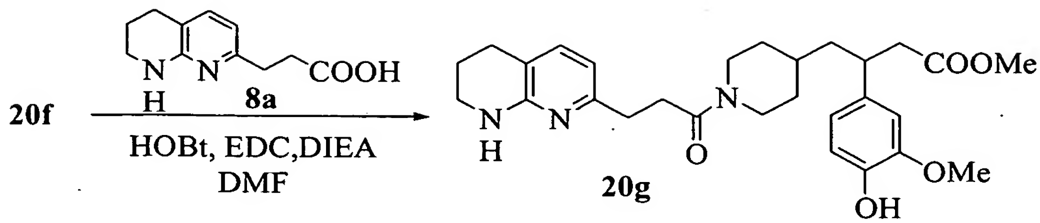
Using the procedure described in Example 12 for converting Compound **12f** to

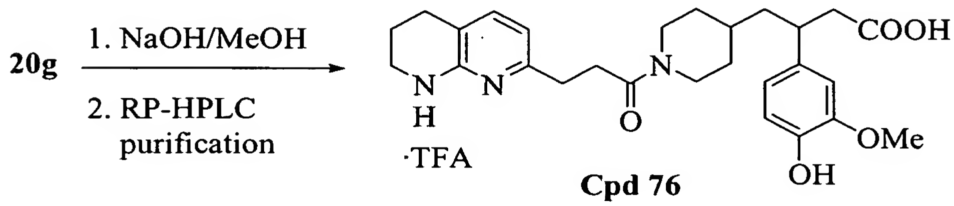
Compound **12g**, Compound **20e** was converted to Compound **20f**. MS (ES+) m/z 308.1 ($M+H^+$).

Using the procedure described in Example 12 for converting Compound **12g** to Compound **12h**, Compound **20f** was converted to Compound **20g**. MS (ES+) m/z 496.8 ($M+H^+$).

Using the procedure described in Example 12 for converting Compound **12h** to Compound **11**, Compound **20g** was converted to Compound **76**. MS (ES+) m/z 482.4 ($M+H^+$). ^{1}HNMR (DMSO-d_6, 300 MHz) δ 0.93 (m, 2H), 1.25 (m, 1H), 1.5 (m, 3H), 1.8 (m, 3H), 2.47 (m, 6H), 2.72 (m, 3H), 2.83 (d, J = 7.3 Hz, 2H), 2.99 (m, 1H), 3.40 (br s, 2H), 3.74 (s, 3H), 3.77 (dd, J = 14.7 Hz, J = 14.3 Hz, 1H), 4.28 (dd, J = 14.7 Hz, J = 14.3 Hz, 1H), 6.60 (d, J = 8.1 Hz, 1H), 6.63 (d, J = 7.2 Hz, 1H), 6.66 d, J = 8.1 Hz, 1H), 6. 77 (br s, 1H), 7.59 (d, J = 7.2 Hz, 1H), 8.04 (br s, 1H).







Derivatives in which the hydroxyl substituent of Compound 76 is alkylated or acylated can be made using general methods, starting materials, and reagents known to one skilled in the art.

<u>Example 21</u>

3-(3-Methylamino-phenyl)-4-[1-(3-5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl-propionyl)-piperidin-4-yl]-butyric acid (Cpd **79**)

A solution of 3-bromoaniline Compound **21a** (2 mL, 18.4 mmol), di-tert-butyl dicarbonate (4.05g, 18.6 mmol) in THF (20 mL) was heated to reflux for 30 h under N_2. The mixture was evaporated under reduced pressure, and the residue was dissolved in EtOAc. The solution was washed with saturated $NaHCO_3$ solution and brine. The organic layer was dried over $MgSO_4$, filtered, and evaporated, to yield Compound **21b**. MS (ES+) m/z 256.8/258.8 (M-CH_3).

Sodium hydride (60% in oil; 0.78g, 19.5 mmol) was added in small portions to a solution of Compound **21b** (4.18g, 15.4 mmol) and methyl iodide (1.21 mL, 19.5 mmol) in DMF (50 mL) at 0 °C. The resulting mixture was allowed to warm to rt and stirred for 1 h. The mixture was poured in ice-water and extracted with EtOAc. The organic layer was separated, dried over $MgSO_4$, filtered, and evaporated under reduced pressure to yield Compound **21c**. MS (ES+) m/z 270.9/272.9 (M-CH_3).

Using the procedure described in Example 12 for converting Compound **12b** to Compound **12d**, Compound **21c** was converted to Compound **21d**. MS (ES+) m/z 455.0 (M+Na$^+$).

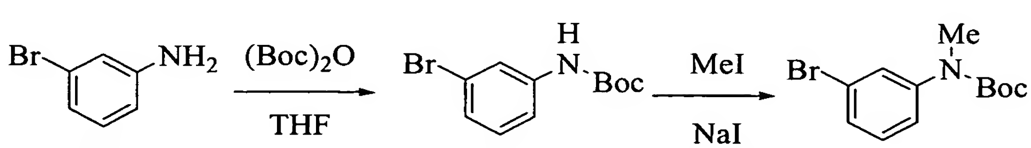
Using the procedure described in Example 12 for converting Compound **12d** to Compound **12e**, Compound **21d** was converted to Compound **21e**. MS (ES+) m/z 510.9 (M+Na$^+$).

Using the procedure described in Example 12 for converting Compound **12e** to Compound **12f**, Compound **21e** was converted to Compound **21f**. MS (ES+) m/z 512.8 (M+Na$^+$).

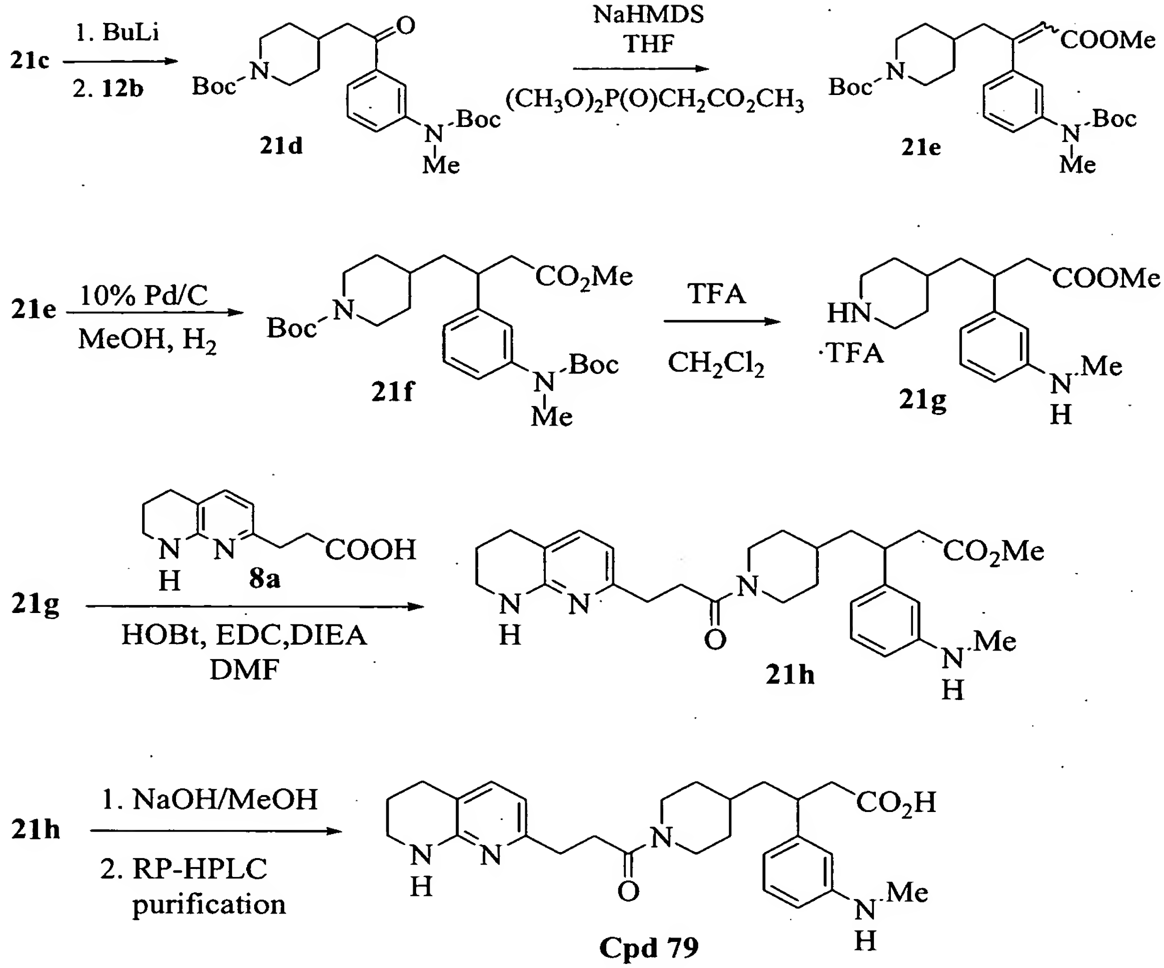
Using the procedure described in Example 12 for converting Compound **12f** to Compound **12g**, Compound **21f** was converted to Compound **21g**. MS (ES+) m/z 291.0 (M+H$^+$).

Using the procedure described in Example 12 for converting Compound **12g** to Compound **12h**, Compound **21g** was converted to Compound **21h**. MS (ES+) m/z 479.0 (M+H$^+$).

Using the procedure described in Example 12 for converting Compound **12h** to Compound **11**, Compound **21h** was converted to Compound **79**. MS (ES+) m/z 465.0 (M+H$^+$). ^{1}HNMR (DMSO-d_6, 300 MHz) δ 0.99 (m, 2H), 1.21 (m, 1H), 1.4-1.65 (m, 3H), 1.72 (m, 1H), 1.86 (m, 2H), 2.3-3.0 (m, 13H), 3.17 (m, 1H), 3.42 (m, 2H), 3.87 (dd, J = 17.7 Hz, J = 15.2 Hz, 1H), 4.40 (dd, J = 15.2 Hz, J = 11.6 Hz, 1H), 6.41 (d, J = 7.5 Hz, 1H), 7.1-7.4 (m, 5H).



21a **21b** **21c**



Using the procedure of Example 21 and the appropriate reagents and starting materials known to those skilled in the art, other compounds of the present invention may be prepared including, but not limited to:

Cpd	Name	MS (m/z)
78	3-(3-Ethylamino-phenyl)-4-[1-(3-5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl-propionyl)-piperidin-4-yl]-butyric acid	479.0

Example 22

3-Naphthalen-2-yl-4-[1-(3-5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl-propionyl)-piperidin-4-yl]-butyric acid (Cpd **56a**)

Using the procedure described in Example 19 for converting Compound **12b** to Compound **19b,** Compound **12b** was converted to Compound **22a** upon reaction with 2-bromonaphthalene. MS (ES+) m/z 376 ($M+Na^+$).

Using the procedure described in Example 19 for converting Compound **19b** to Compound **19c**, Compound **22a** was converted to Compound **22b**. MS (ES+) m/z 432.1 ($M+Na^+$).

Using the procedure described in Example 19 for converting Compound **19c** to Compound **19d**, Compound **22b** was converted to Compound **22c**. MS (ES+) m/z 434.1 ($M+Na^+$).

Racemic Compound **22c** was separated into the two enantiomerically pure Compounds **22d** and **22e** on a chiral column using ethanol as eluent (Stationary phase: Chiralpak AD 20 μm (Daicel); column diameter: 50 mm; detector: 0.5 mm Knauer superpreparative cell; wavelength: 225 nm). **22d** (first eluting isomer): $[\alpha]^{20}_{D}$ +0.177 (*c* 0.75, MeOH). **22e** (second eluting isomer): $[\alpha]^{20}_{D}$ –0.167 (*c* 0.683, MeOH).

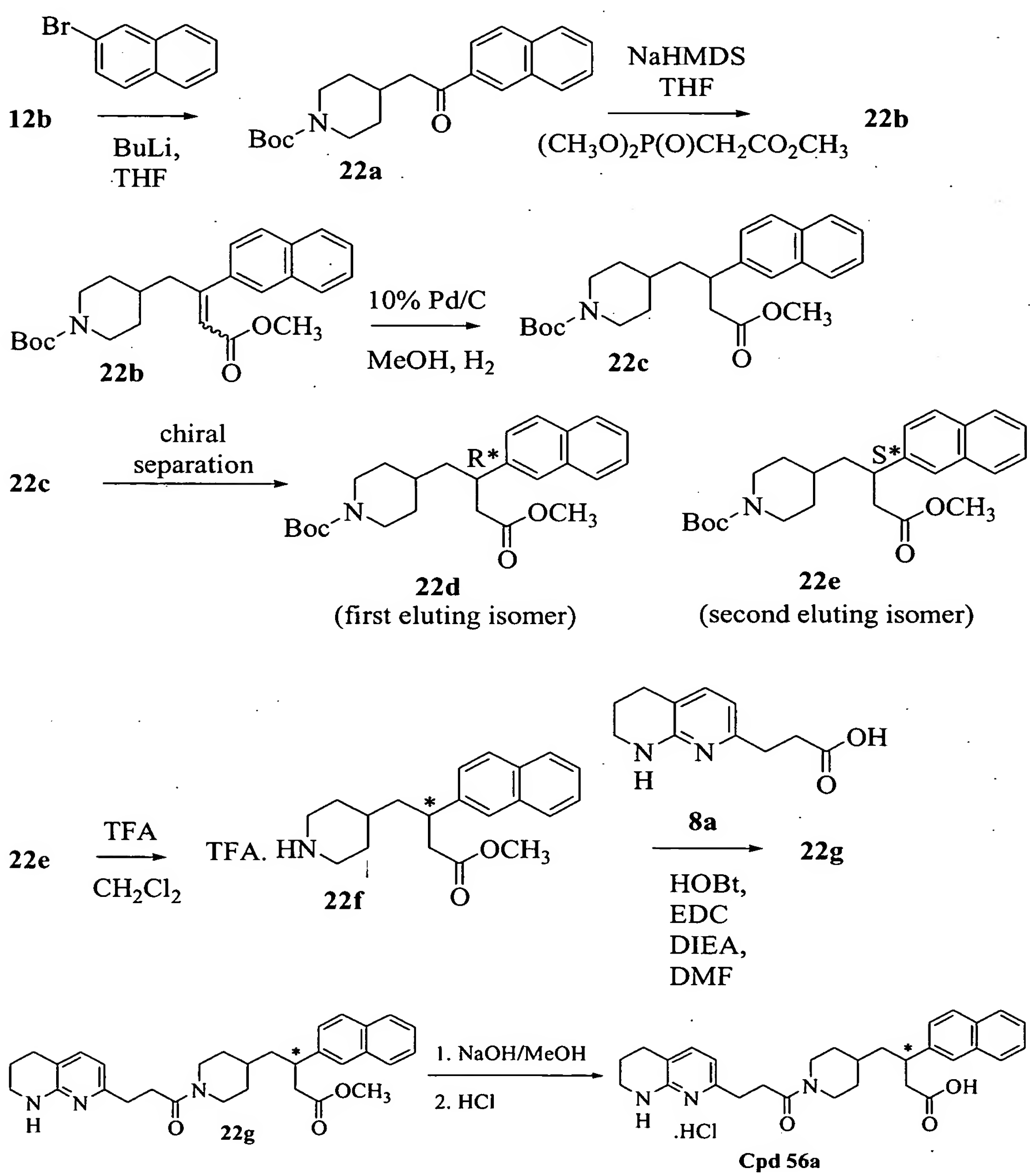
Using the procedure described in Example 19 for converting Compound **19f** to Compound **19g**, Compound **22e** was converted to Compound **22f**. MS (ES+) m/z 312.0 ($M+H^+$).

Using the procedure described in Example 19 for converting Compound **19g** to Compound **19h**, Compound **22f** was reacted with Compound **8a** to yield Compound **22g**. MS (ES+) m/z 500.0 ($M+H^+$).

Using the procedure described in Example 19 for converting Compound **19h** to Compound **36a**, Compound **22g** was converted to Compound **56a** . MS (ES+) m/z 486.0($M+H^+$). ^{1}HNMR ($CDCl_3$, 300 MHz) δ 0.95-1.35 (m, 3H), 1.44-2.0 (m, 6H), 2.35 (t, J = 12.7 Hz, 1H), 2.55-3.1 (m, 9H), 3.40 (m, 3H), 3.89 (m, 1H), 4.42 (m, 1H), 6.45 (d, J = 7.4 Hz, 1H), 7.24 (d, J = 7.4 Hz, 1H), 7.35 (d, J = 8.1 Hz, 1H), 7.45 (m, 2H),

7.65 (s, 1H), 6.45 (d, $J = 7.4$ Hz, 1H), 7.7-7.85 (m, 3H). Anal. Calcd for $C_{30}H_{35}N_3O_3$-1.1 HCl-0.75 H_2O: C, 66.83; H, 7.03; N, 7.80; Cl, 7.24; H_2O, 2.51. Found: C, 66.53; H, 7.26; N, 8.15; Cl, 7.27; H_2O, 2.39. $[\alpha]^{20}_D$ −0.193 (*c* 0.717, MeOH).

Enantiomer **56b** was obtained from the fast moving enantiomer **22d** using procedures described for converting **22e** to Compound **56a**.



Example 23

3-(3-Fluoro-phenyl)-4-[1-(3-5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl-propionyl)-piperidin-4-yl]-butyramide (Cpd **64**)

Using the procedure described in Example 12 for converting Compound **12b** to Compound **12d**, Compound **12b** was converted to Compound **23a** upon reaction with 1-bromo-3-fluorobenzene. MS (ES+) m/z 344 ($M+Na^+$).

Using the procedure described in Example 12 for converting Compound **12d** to Compound **12e**, Compound **23a** was converted to Compound **23b** upon reaction with Diethyl cyanomethylphosphonate. MS (ES+) m/z 367.4 ($M+Na^+$).

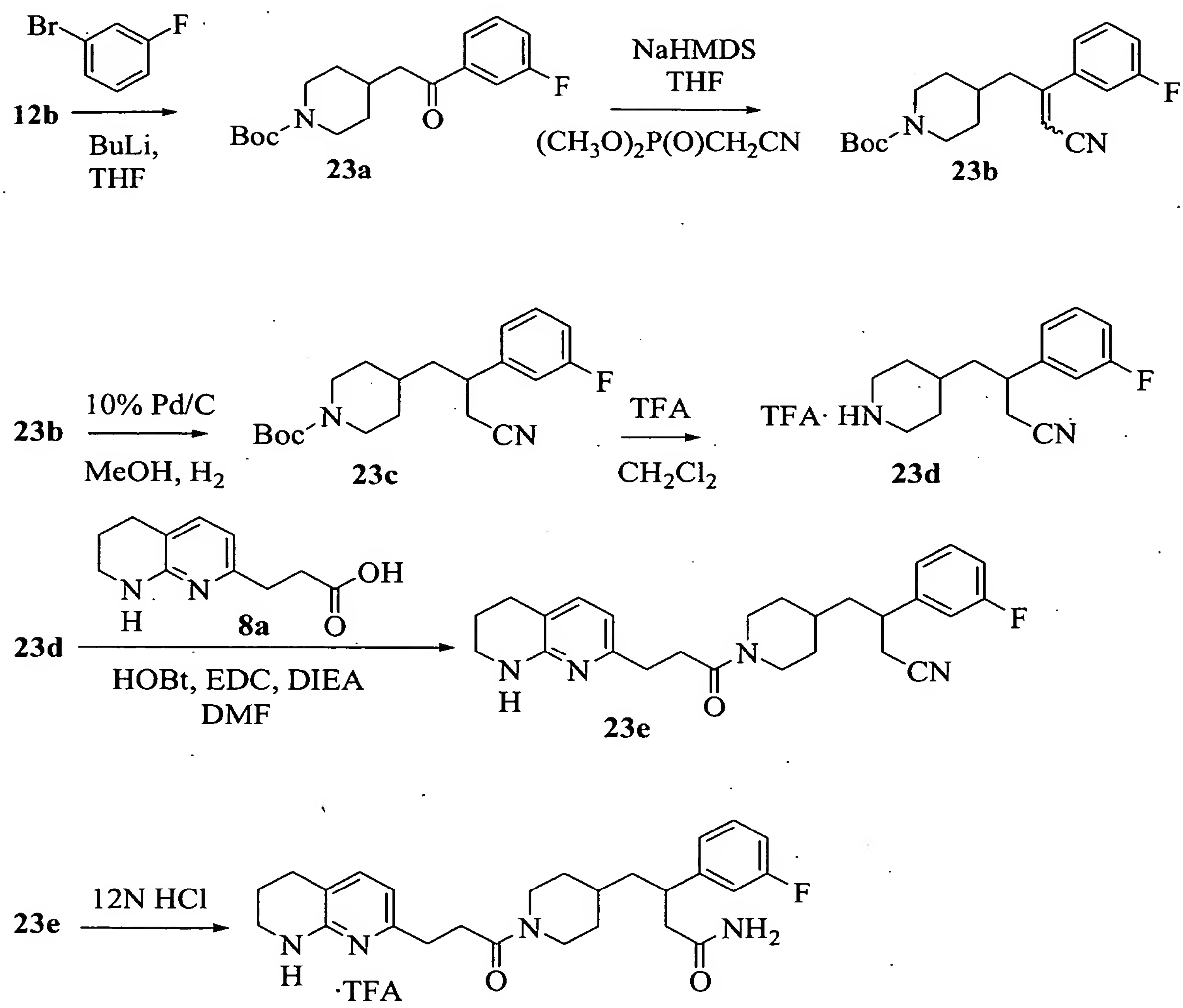
A solution of of Compound **23b** (2.06g, 5.98 mmol) in EtOH (50 mL) was hydrogenated at 5 psi in the presence of 10% palladium on carbon (200 mg) for 40 h. The catalyst was removed by filtration over celite. The filtrate was concentrated *in vacuo* to yield Compound **23c**. MS (ES+) m/z 369.5 ($M+Na^+$).

Using the procedure described in Example 12 for converting Compound **12f** to Compound **12g**, Compound **23c** was converted to Compound **23d**. MS (ES+) m/z 247 ($M+H^+$).

Using the procedure described in Example 12 for converting Compound **12g** to Compound **12h**, Compound **23d** was reacted with Compound **8a** to yield Compound **23e**. MS (ES+) m/z 435 ($M+H^+$).

A mixture of Compound **23e** (150 mg, 0.345 mmol) and 12N HCl (10 mL) was heated to 40 °C for 3 h. The mixture was evaporated to dryness and further dried by lyophilization to yield Compound **64**. MS (ES+) m/z 453.5 ($M+Na^+$). ^{1}HNMR (DMSO-d_6, 300 MHz) δ 0.8-1.1 (m, 2H), 1.25 (m, 1H), 1.4-1.65 (m, 3H), 1.7-1.9 (m, 4H), 2.25-2.5 (m, 4H), 2.7-2.9 (m, 8H), 3.21 (m, 1H), 3.82 (t, J = 13.6 Hz, 1H), 4.31 (t, J = 13.6 Hz, 1H), 6.66 (d, J = 7.3Hz, 1H), 6.71 (br s, 1H), 6.95-7.15 (m, 3H), 7.25 (br s,

1H), 7.36 (dd, J = 15.1 Hz, J = 7.3 Hz, 1H), 7.63 (d, J = 7.3 Hz, 1H), 7.98 (br s, 1H), 13.77 (br s, 1H).



Cpd 64

<u>Example 24</u>

3-(3-Fluoro-phenyl)-4-[1-(3-5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl-propyl]-piperidin-4-yl]-butyric acid (Cpd **81**)

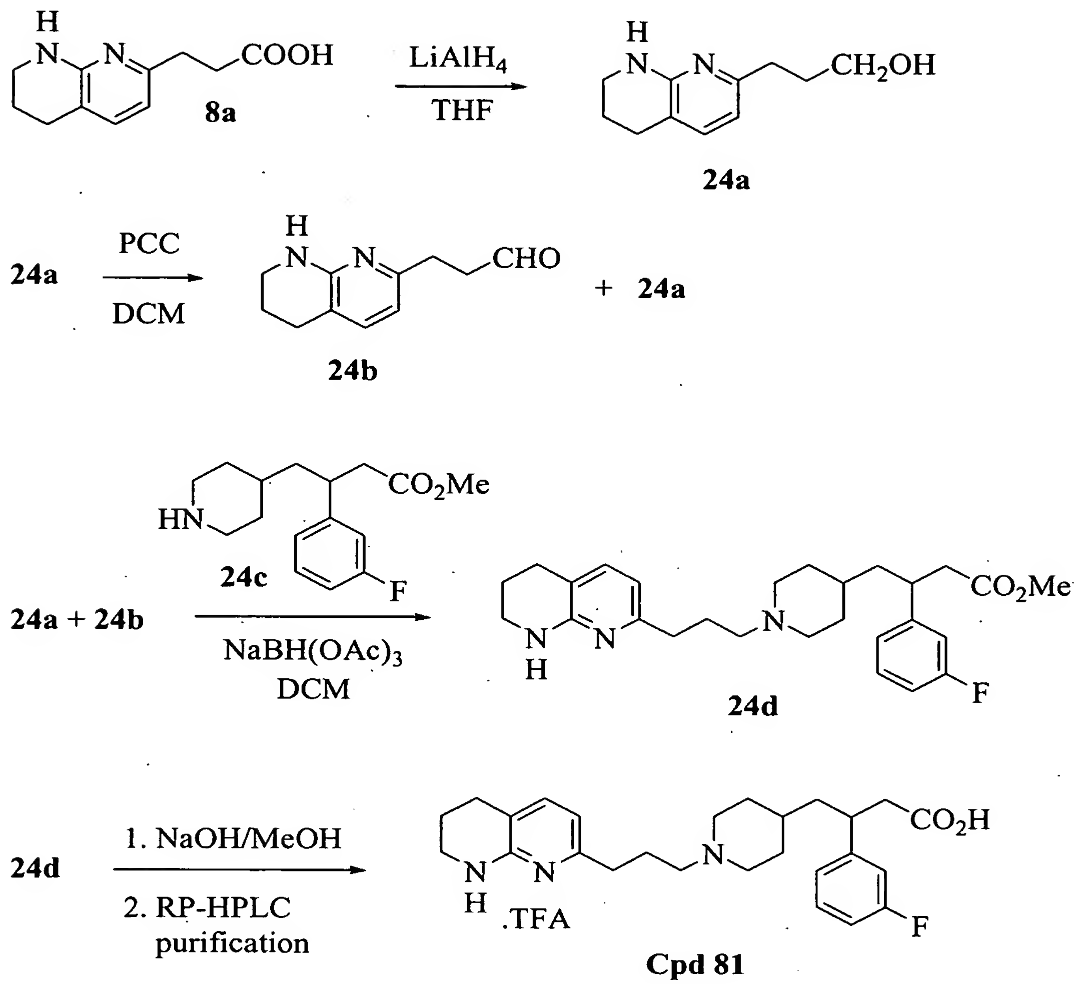
Lithium aluminum hydride (1.0M in THF; 16.5 mL, 16.5 mmol) was added slowly to a suspension of Compound **8a** (2.0g, 8.2 mmol) in dry THF (60 mL) at 0 °C. The cooling bath was removed, and the mixture was stirred for 24 hr at rt. The mixture was quenched with water and celite was added. The mixture was extracted with Et_2O and

EtOAc. The organic phase was dried over Na_2SO_4, filtered, and concentrated under reduced pressure, yielding Compound **24a**. MS (ES+) m/z 193.2 ($M+H^+$).

Compound **24a** (0.5g, 2.6 mmol) was added to a suspension of pyridinium chlorochromate (0.67g, 3.12 mmol) in DCM (5 mL). The mixture was stirred overnight at rt. Diethyl ether was added, and the mixture was filtered. The filtrate was dried over Na_2SO_4. After removal of the drying agent via filtration, the solvent was removed under reduced pressure, yielding a mixture of **24a** and **24b** that was used as such for the next reaction. Compound **24b**: MS (ES+) m/z 191.1 ($M+H^+$).

Sodium triacetoxyborohydride (25.6 mg, 0.074 mmol) was added to a mixture of **24a** and **24b** (0.01g, 0.05 mmol) and piperidine Compound **24c** (0.015g, 0.05 mmol; obtained using the procedure described in Example 12 for converting Compound **12a** to Compound **12g**, and wherein bromo-3-fluorobenzene was substituted for the 4-bromo-1,2-(methylenedioxy)benzene (Compound **12c)** and was reacted to form a 3-fluorophenyl compound analogous to compound **12f)** in DCM (0.2 mL) and the mixture was stirred for 4 hr at rt. Diethyl ether was added, and the organic layer was separated and dried over Na_2SO_4. The drying agent was removed by filtration, and the solvent was removed under reduced pressure. The residue was purified via column chromatography (eluent gradient: DCM:MeOH:NH_4OH; 100:0:0 to 90:9:1) to yield Compound **24d**. MS (ES+) m/z 454.4 ($M+H^+$).

Using the procedure described in Example 12 for converting Compound **12h** to Compound **11**, Compound **24d** was converted to Compound **81**. MS (ES+) m/z 440.5 ($M+H^+$).



<u>Example 25</u>

β-(3-fluorophenyl)-1-[1-oxo-3-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)propyl]-4-piperidinebutanoic acid (Cpd **30a and 30b**)

Compound **30** was synthesized following the process set forth in Example 12 wherein bromo-3-fluorobenzene was substituted for the 4-bromo-1,2-(methylenedioxy)benzene (Compound **12c)** and was reacted to form a 3-fluorophenyl compound analogous to compound **12f.**

Additional Compound **30** was resolved into two isomers (Cpd **30a** and Cpd **30b**) by generally following the procedure set in Example 19, wherein the stationary phase was Chiralcel OD; eluent: hexane/EtOH: 95/5; wavelength: 220 nm. The isomer of most

interest was the second eluting isomer. The separated isomers were converted into Compounds **30a** and **30b** by completion of the synthesis from Compound **12f** on as set forth in Example 12 to yield Compounds **30a** and **30b**.

Prospective Example 26

3-(2,3-Dihydro-benzofuran-6-yl)-4-[1-(3-5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl-butyl)-piperidin-4-yl]-propanoic acid (Cpd **80**)

Using the procedure described in Example 3 for converting Compound **3b** to Compound **3c**, Compound **3b** may be converted to provide Compound **26a** when reacted with 6-bromo-2,3-dihydrobenzofuran.

Using the procedure described in Example 3 for converting Compound **3c** to Compound **3d**, Compound **26a** may be converted to provide Compound **26b**.

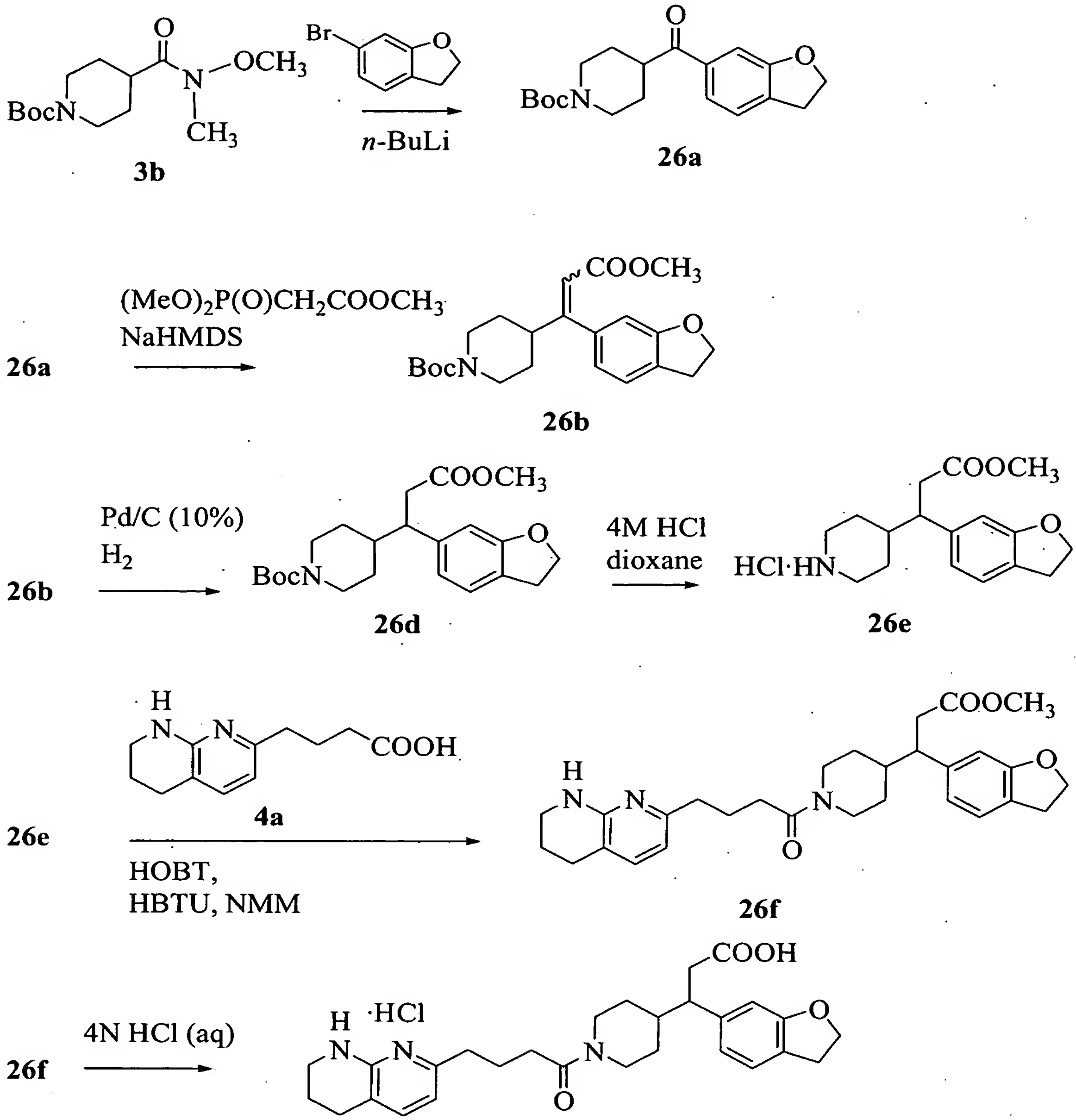
Using the procedure described in Example 3 for converting Compound **3d** to Compound **3e**, Compound **26b** may be converted to provide Compound **26c**.

Using the procedure described in Example 3 for converting Compound **3e** to Compound **3f**, Compound **26c** may be converted to provide Compound **26d**.

Using the procedure described in Example 3 for converting Compound **3f** to Compound **3g**, Compound **26d** may be converted to provide Compound **26e**.

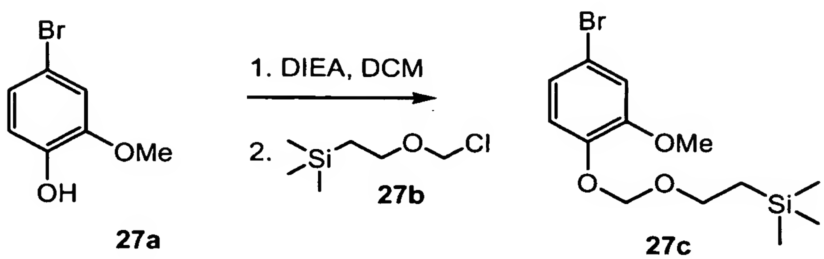
Using the procedure described in Example 4 for converting Compound **4a** to Compound **4b**, Compound **26e** may be converted to provide Compound **26f**.

Using the procedure described in Example 4 for converting Compound **4b** to Compound **4**, Compound **26f** may be converted to provide Compound **80**.



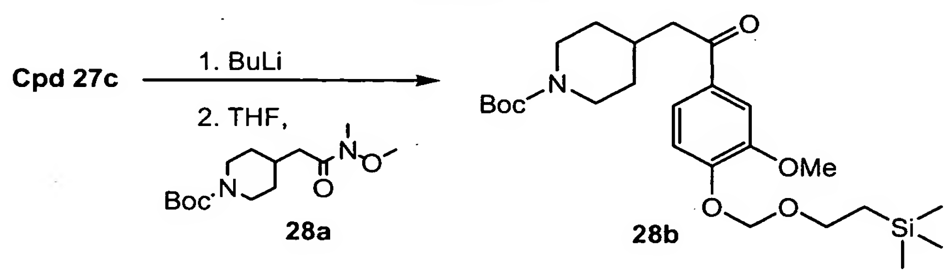
Cpd 80

Example 27



A sample of Compound **27a** (78.2 g, 385 mmol) and diisopropylethylamine (DIEA) (54.8 g, 424 mmol, 73.8 mL) was dissolved into dry CH_2Cl_2 (700 mL) and Compound **27b** (70.7 g, 424 mmol, 75 mL) was added dropwise. After 16 h while stirring at ambient temperature, brine (500 mL) was added. The phases were separated and the aqueous phase extracted with CH_2Cl_2 (300 mL). The organic phases were combined and dried over sodium sulfate. The mixture was concentrated and the residue, an orange semisolid, was applied to a flash column (silica gel, 6 x 20 cm). The residue was eluted with heptane (500 mL), followed by 10% EtOAc/ heptane (2 L) in 500 mL fractions. Fractions 1 and 2 gave pure Compound **27c**. A second purification was required on fractions 3 and 4 using the chromatography conditions described above. The crops were combined to give 112 g of Compound **27c**: ^{1}H NMR ($CDCl_3$) δ: 7.1-7.0 (m, 3H), 3.9 (s, 3H), 3.8 (t, 2H) 0.9 (t, 2H) and 0.0 ppm (s, 9H).

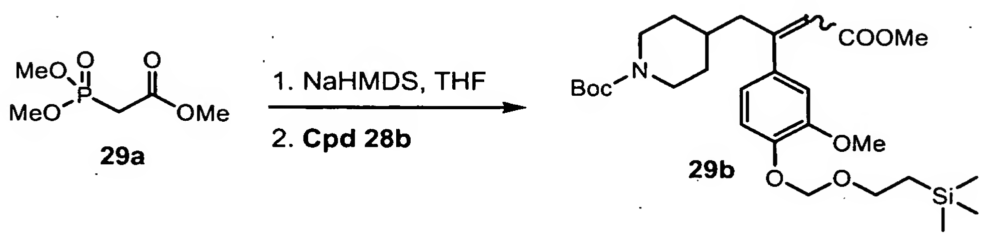
Example 28



Compound **27c** (112.2 g, 330.7 mmol) was dissolved in dry THF (1.3 L). The colorless solution was cooled down to -75 °C and 2.5M *n*-butyllithium (120.3 mL, 300.6 mmol) in hexanes was added through an addition funnel. After 15 min stirring at -75°C, a solution of Compound **28a** (86.09 g, 300.6 mmol) in dry THF (500 mL) was added dropwise over 2 h with an addition funnel at –75 °C. During the addition, the colorless solution turned light green, and then became yellow. HPLC analysis indicated that the reaction had gone to completion 20 min after complete addition of Compound **28a**. The reaction was quenched with saturated ammonium chloride (100 mL), then allowed to come to ambient temperature overnight. The organic phase was isolated, washed with brine (250 mL), and the aqueous phase was extracted with diethyl ether (2

x 150 mL). The combined organic phases were dried over sodium sulfate and then concentrated. The resultant pale yellow residue was divided into two batches and applied separately to a flash chromatography column (silica gel, 10 cm for the first batch/ 8 cm for the second; fitted funnel 6 cm wide) with applied vacuum. The first batch of Compound **28b** was eluted with heptane (2 L), followed by a gradient of heptane/ EtOAc: 95/5 (2L), 90/10 (4L), 80/20 (4L), and 70/30 (4L). The second batch was eluted with heptane (1L), followed by heptane/ EtOAc 9/1 (2L), 85/15 (2L), and 80/20 (2L). The fractions were combined and evaporated to give 109 g of Compound **28b**: ^{1}H NMR ($CDCl_3$) δ: 7.5 (m, 2H), 7.2 (d, 1H), 4.2-4.0 (broad m, 2H), 3.95 (s, 3H), 3.8 (t, 2H), 2.85 (d, 2H), 2.8-2.7 (broad t, 2H), 2.15 (broad m, 1H), 1.7 (broad d, 2H), 1.45 (s, 9H), 1.3-1.1 (broad m, 2H), 0.9 (t, 2H) and 0.0 ppm (s, 9H).

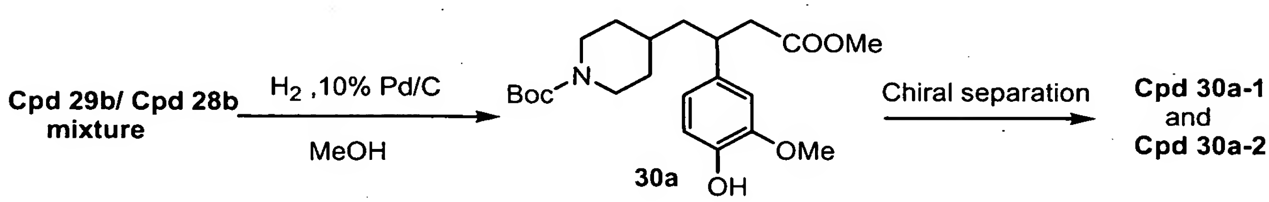
Example 29



Compound **29a** (trimethyl phosphonoacetate) (124.12 g, 681.6 mmol, 112.5 mL) in 50 mL of dry THF was cooled to 0 °C and NaHMDS in THF (1.0 M, 681.6 mL) was added at 0 °C in three equal portions with mechanical stirring. After the addition of the first portion, the solution became a thick beige slurry and the consistency remained unchanged throughout the duration of the addition. The slurry was stirred at 0 °C for 1 h after which time Compound **28b** (109.0 g, 227.2 mmol) was added in one portion as a suspension in dry THF (250 mL). The reaction mixture was then heated to reflux for 96 h. At this time the reaction was cooled to ambient temperature and saturated ammonium chloride (400 mL) was added. The phases were separated and the aqueous phase washed with ether (2 x 300 mL). The combined organic phases were dried over sodium sulfate, filtered and the solvent evaporated. The resulting residue was poured onto a fritted glass funnel containing a pad of flash silica gel (diameter: 15 cm, height: 8 cm). The compound was isolated by first eluting with pure heptane (2L) then with a gradient of heptane/ EtOAc: 90/10 (2 L), 80/20 (4 L), and 70/30 (4 L),

collecting in fractions of 1.8 L. Compound **29b** was isolated as a mixture of *E*/*Z* isomers, and was contaminated with unreacted Compound **28b** (33% by HPLC, 120 g total of mixture). The mixture was carried on to the next step without further purification.

Example 30



The mixture of **Cpd 29b** and **Cpd 28b** (120 g total), as prepared in Example 29, was dissolved in MeOH (1 L) and, under a stream of Argon, 10% Pd-C catalyst (3.0 g) was added. The mixture was shaken in a Parr® apparatus under an atmosphere of H_2 gas (35 psi) for 18 h at ambient temperature. At this time, LC/ MS analysis of the reaction indicated that Compound **29b** had been converted to Compound **30a**. After thoroughly purging with Argon gas, the reaction mixture was filtered through a pad of Celite and the solvent was removed in vacuo. The resultant residue was applied to a flash column (silica gel, 15 cm x 8 cm) in a fritted glass funnel and eluted with a gradient of pure heptane (2L) followed by mixtures of heptane/ EtOAc: 90/10 (2L), 80/20 (4L), 70/30 (4L), collecting in 1.8 L fractions. Upon evaporation, Compound **30a** was isolated as a white foam (47.5 g). ^{1}H NMR ($CDCl_3$) δ: 6.9-6.6 (m, 3H), 5.6 (s, 1H), 4.2-4.0 (m, 2H), 3.9 (s, 3H), 3.6 (s, 3H) 3.2-3.1 (m, 1H), 2.6-2.5 (m, 4H), 1.8-1.0 (m, 7 H) and 1.4 ppm (s, 9H).

Compound **30a** was separated into its pure enantiomers by chiral chromatography according to the method described herein.
The separation of Compound **30a** was performed on a 5 cm Chiralpak AD column at a flow of 1 mL/min. Monitoring was performed at λ= 220 nm, and the eluent was a mixture of heptane/ EtOH/ MeOH (92:4:4). The faster eluting enantiomer of Compound **30a**, Compound **30a-1** (12.96 g) proved to be the less avid binding ligand

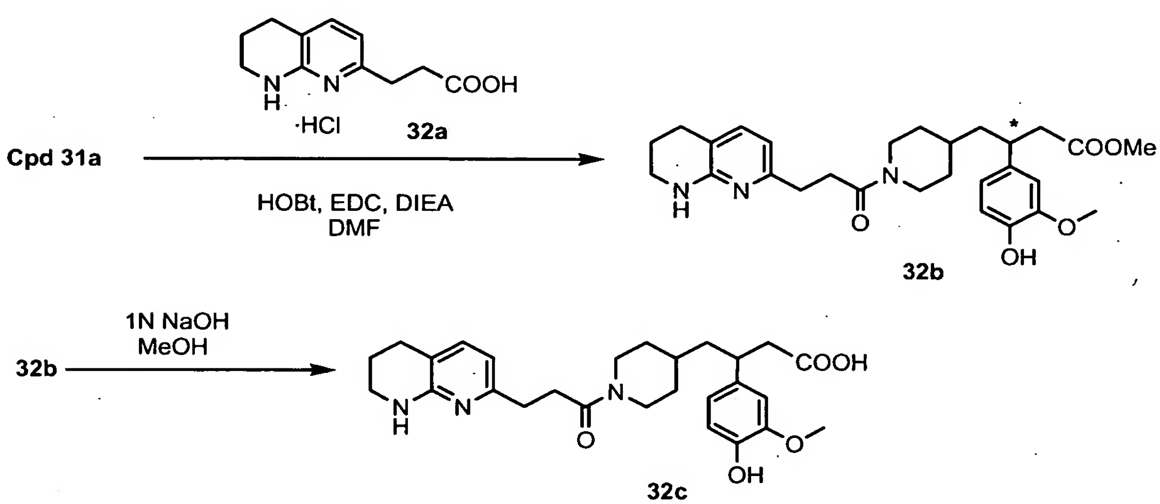
for the $\alpha_V\beta_3$ and $\alpha_V\beta_5$ receptors while the slower eluting enantiomer of Compound **4a**, Compound **30a-2** (17.62 g) gave the more potent binding ligands (see the section below). Therefore, the slower eluting enantiomer Compound **30a-2** was carried forward for use in the preparation of subsequent optically active compounds, unless noted otherwise.

Example 31

Cpd 30a-1 → 31a

Compound **30a-1** (12.96 g) was dissolved into 25 mL of dry DCM and TFA (10.0 mL) was added. After stirring for 1 h at ambient temperature, the reaction mixture was evaporated. The residue was co-evaporated with chloroform (3 x) and DCM (2 x) to give Compound **31a** as a TFA salt (12.56 g).

Example 32



A mixture of Compound **32a** (3.77g, 15.55 mmol), Compound **31a** (5.46 g,

12.96 mmol), HOBt (1.93 g, 14.25 mmol), DIEA (8.14 g, 63.0 mmol, 11.0 mL) and EDC (2.73 g, 14.25 mmol) were dissolved into dry DMF (200 mL). After 96 h at ambient temperature, the reaction was diluted with water (500 mL) and the mixture was extracted with EtOAc (4 x 300 mL). The combined organic phases were washed with brine (5 x 300 mL) then dried over sodium sulfate and evaporated. The residue was purified on a flash column (silica gel, 6 x 20 cm) by eluting with DCM (1L), followed by a gradient of DCM/ 10% NH_4OH in MeOH: 95/5 (2L), 90/10 (2L), 85/15 (2L). The fractions were collected in the following volumes: 1 to 3: 500 mL each, 4 to 19: 200 mL each, and 20: 500 mL.

Compound **32b** was isolated as a foam.

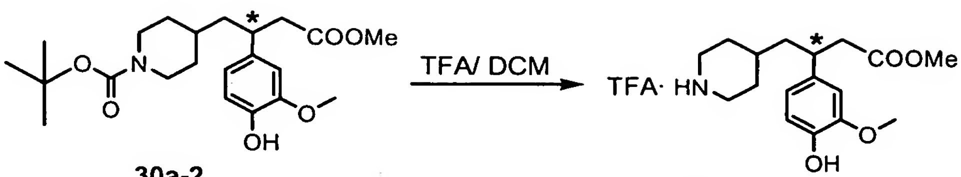
Compound **32b** (325 mg) was dissolved in 1N NaOH (1.3 mL) and MeOH (2.6 mL). After stirring for 18 h at room temperature, the solution was neutralized with 2N HCl (0.400 mL). The reaction mixture was transferred to a test tube, rinsing with MeOH, and purified in several separate runs by HPLC (12 min per run; 35 mL/ min) eluting with 15-35% CH_3CN: H_2O/ 0.1 % TFA on a C18 reverse phase column (100 x 30 mm). Compound **32c** was obtained as a light yellow powder (195 mg): LRMS m/z 481.26; ^{1}H NMR ($CDCl_3$) δ: 9.5 (broad s, 1H), 7.5-7.3 (m, 5 H), 6.8 (d, 1H), 6.7 (s, 2H), 6.45 (d, 1H), 4.45 (t, 1H), 4.1-3.9 (m, 1H), 3.8 (s, 3H), 3.5 (broad s, 2H), 3.1 (broad m, 1H), 3.0-2.6 (m, 4H), 2.55 (d, 2H), 2.45 (t, 1H), 1.9 (broad s, 3H), 1.7-1.4 (m, 3H), 1.25 (m, 1H) and 1.1-0.9 ppm (m, 2H).

Compound **32c** was tested in the $\alpha_V\beta_3$ and $\alpha_V\beta_5$ binding assays described in Biological Example 4 with the following results:

ASSAY	RESULT FOR **Cpd 32c**
$\alpha_V\beta_3$ Binding Affinity	IC_{50} = 104 nM
$\alpha_V\beta_5$ Binding Affinity	IC_{50} = 2,313 nM

Based on the poor receptor binding affinity of Compound **32c** relative to Compound **35c** (see below), Compound **32c** was not investigated any further for its potential as a targeting ligand.

Example 33

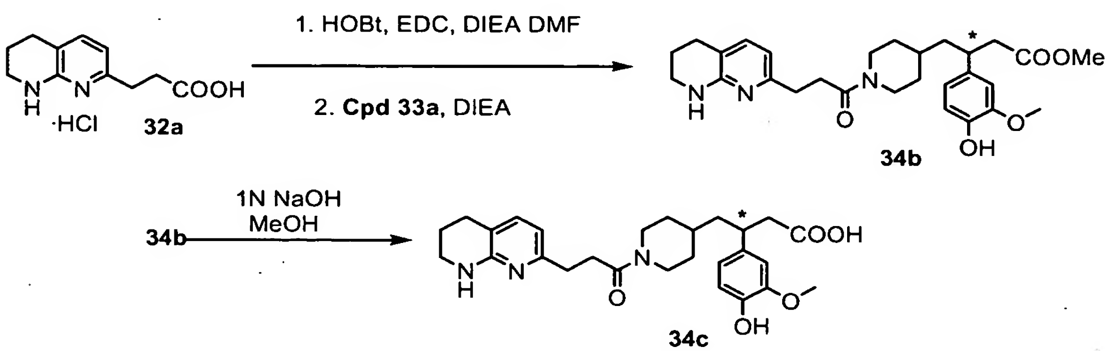


30a-2

33a

Compound **30a-2** (17.6 g, 43.3 mmol), the slower eluting enantiomer of Example 30, was dissolved into 30 mL of dry DCM and TFA (15.0 mL) was added. After 1.5 h of stirring at ambient temperature, the reaction mixture was evaporated. The residue was co-evaporated with chloroform (3 x) and DCM (2 x) and stored *in vacuo* to obtain Compound **33a** as its TFA salt as a yellow solid (16.5 g).

Example 34



32a

34b

34c

A mixture of Compound **32a** (11.75 g, 48.41 mmol), HOBt (5.99 g, 44.33 mmol), DIEA (13.02 g, 100.8 mmol, 17.55 mL) and EDC (8.49 g, 44.3 mmol) were dissolved into dry DMF (200 mL). This mixture was stirred at ambient temperature for 1.5 h then a solution of Compound **33a** (17.0 g, 40.3 mmol) and DIEA (13.02 g, 100.75 mmol, 17.55 mL) in DMF (100 mL) was added. After 140 h (~ 6 d) of stirring at ambient temperature, the reaction mixture was diluted with water (900 mL). The diluted reaction mixture was extracted with EtOAc (4x 300 mL). The combined organic phases were washed with brine (5

x 300 mL) then dried over sodium sulfate and evaporated. The residue was purified on a flash chromatography column (silica gel, 6 x 20 cm), eluting first with DCM (800 mL) and then with a gradient of DCM/ 10% NH_4OH (0.1 %, aq) in MeOH in the following proportions: 95/5 (2L), 90/10 (2L), 80/20 (2L). The fractions were collected in 300 mL volumes. The fractions were concentrated to give 980 mg of Compound **34b** as a red oil. An impure sample of Compound **34b** was recovered from other fractions (6.17 g).

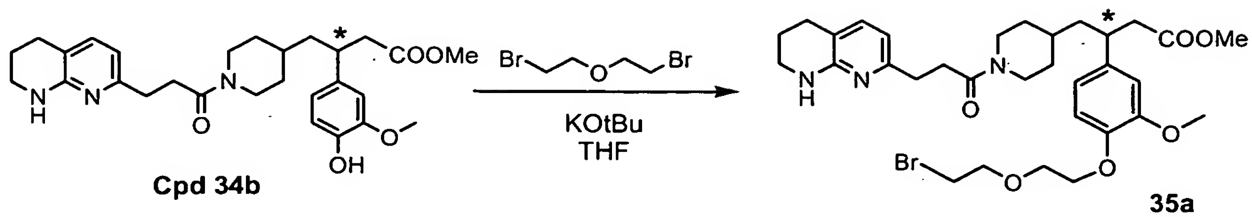
Compound **34b** (435 mg) was stirred with 3N NaOH (0.700 mL) in MeOH (2.0 mL). After 15 h of stirring at ambient temperature, 2N HCl was added to neutralize the solution (1.0 mL). The red solution was transferred into a test tube, rinsing with MeOH, and purified in several separate HPLC runs (12 min per run; 35 mL/ min) eluting with a gradient of 15-35% CH_3CN: H_2O/ 0.1 % TFA on a C18 reverse phase column (100 x 30 mm). Lyophilization of the fractions provided Compound **34c** (378 mg) as a light yellow powder: LRMS m/z: 481.26; ^{1}H NMR ($CDCl_3$) δ: 9.7 (broad s, 1H), 7.3 (d, 1H), 6.9 (d, 1H), 6.7 (d, 1H), 6.7 (s, 1H), 6.5 (d, 1H), 6.4-6.0 (broad s, 3H), 4.5 (t, 1H), 4.1-3.9 (m, 1H), 3.9 (s, 3H), 3.5 (broad s, 2H), 3.1 (m, 1H), 3.0-2.7 (m, 6H), 2.6 (d, 2H), 2.5 (t, 1H), 2.0-1.8 (m, 3H), 1.7-1.4 (m, 3H), 1.3 (m, 1H) and 1.2-0.9 ppm (m, 2H).

Compound **34c** was tested in the $\alpha_V\beta_3$ and $\alpha_V\beta_5$ binding assays described in Biological Example 4 with the following results:

ASSAY	RESULT FOR **Cpd 34c**
$\alpha_V\beta_3$ Binding Affinity	IC_{50} = 1.1 nM
$\alpha_V\beta_5$ Binding Affinity	IC_{50} = 17 nM

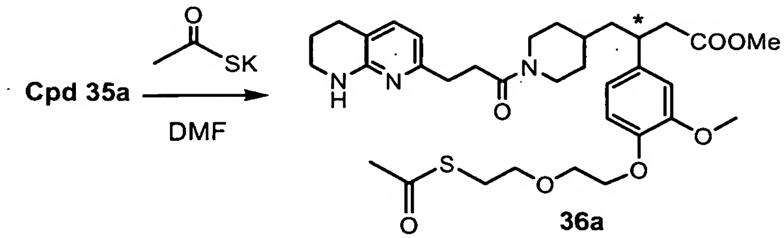
Based on the strong receptor binding affinity of Compound **34c** relative to Compound **34c**, Compound **34c** was chosen for the preparation of targeting ligands.

Example 35

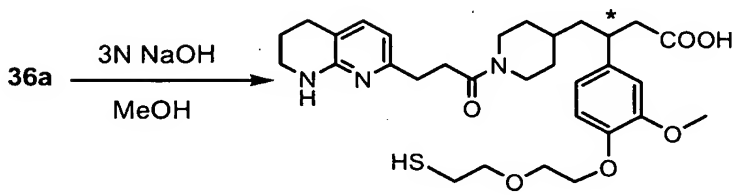


Dibromoethyl ether (2.5 g, 1.35 mL,10.76 mmol) was added to a solution of Compound **34b** (0.48 g, 0.97 mmol) and 1.0 M potassium t-butoxide/ propanol in dry THF (1.5 mmol, 1.5 mL), and the mixture was heated to 70 °C. The reaction reached approximately 50% conversion in the first 30 min and continued to stir. After 5 h, additional 1.0 M potassium t-butoxide solution was added (0.95 mmol, 0.95 mL), and the reaction was completed after 30 min at 70 °C. The reaction was quenched with water and the mixture was extracted with diethyl ether (2 x 100 mL) and DCM (2 x 50 mL). The combined organic extracts were dried over sodium sulfate, evaporated, and the resulting residue was purified by flash column chromatography (silica gel, 4 x 16 cm) by eluting with a gradient of DCM (500 mL), followed by DCM/ 10% NH_4OH (0.1 % aq) in MeOH: 97/3 (1L), then 95/5 (1L). The first fraction collected was a volume of 400 mL, followed by 100 mL fractions for collections 2-15. Concentration of the fractions gave Compound **35a** (318 mg) as an oil; LRMS: 645.24 m/z; ^{1}H NMR ($CDCl_3$) δ: 7.1 (d, 1H), 6.85 (d, 1H), 6.7 (d, 1H), 6.7 (s, 1H), 6.4 (d, 1H), 4.8 (broad s, 1H) 4.5 (t, 1H), 3.9 (t, 4H), 3.8 (s, 3H), 3.6 (s, 3H), 3.5 (s, 3H), 3.4 (m, 2H), 3.1 (m, 1H), 2.9-2.8 (m, 3H), 2.7-2.6 (m, 4H), 2.5 (d, 2H) 2.4 (m, 1H), 1.9 (m, 2H), 1.8 (m, 2H), 1.6-1.4 (m, 3H) 1.2-1.1 (m, 1H) and 1.0 ppm (m, 2H).

Example 36



36a



36b

Potassium thioacetate (0.28 g, 2.46 mmol) was added to a solution of Compound **35a** (0.159 g, 0.246 mmol) in dry DMF (1 mL) and the mixture was heated to 60 °C. After stirring for 1 h at 60 °C, the reaction was cooled to ambient temperature, diluted with water (100 mL), and extracted with EtOAc (3 x 50 mL). The organic phase was dried over sodium sulfate, evaporated, and the resultant residue was purified by flash chromatography (silica gel, 4 x 10 cm). The column was first eluted with EtOAc (3 x 100 mL fractions) then DCM (5 x 100 mL fractions), and finally a gradient of DCM/ 10% NH_4OH (0.1 % aq) in MeOH: 98/ 2 (10 x 50 mL), then 95/ 5 (10 x 50 mL) to yield Compound **36a** (80 mg): LRMS: 641.31 m/z.

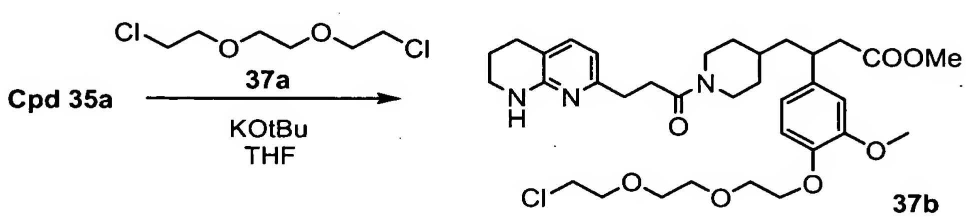
Compound **36a** (approximately 80 mg) was dissolved into MeOH (0.800 mL) and 3N NaOH (0.400 mL) was added. After stirring for 18 h at ambient temperature, the mixture was neutralized with 2N HCl. Purification was performed using several separate HPLC runs (12 min per run, 35 mL/ min), eluting with a gradient of 25-45% CH_3CN: H_2O/ 0.1 % TFA on a C18 reverse phase column (100 x 30 mm). Upon lyophilization, Compound **36b** (60 mg) was obtained as a yellowish powder: LRMS 585.2 m/z; ^1H NMR ($CDCl_3$) δ 9.6 (broad s, 1H), 7.4 (d, 1H), 6.9 (d, 1H), 6.7 (d, 1H), 6.7 (s, 1H), 6.5 (d, 1H), 5.4 (br s, 3H), 4.5 (t, 1H), 4.2 (m, 2H), 4.1-3.7 (m, 4 H), 3.8 (s, 3H), 3.5 (m, 2H), 3.1

(m, 1H), 3.0-2.9 (m, 5 H), 2.8-2.7 (m, 4 H), 2.6-2.4 (m, 3H), 2.0-1.8 (m, 3H), 1.7-1.4 (m, 3 H), 1.3-1.2 (m, 1H), and 1.1-1.0 ppm (m, 2H).

Compound **36b** was tested in the $\alpha_V\beta_3$ and $\alpha_V\beta_5$ binding assays described in Biological Example 4 with the following results:

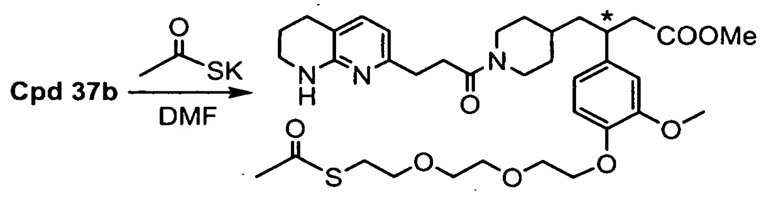
ASSAY	RESULT FOR **Cpd 36b**
$\alpha_V\beta_3$ Binding Affinity	IC_{50} = 0.8 nM
$\alpha_V\beta_5$ Binding Affinity	IC_{50} = 4.8 nM

Example 37

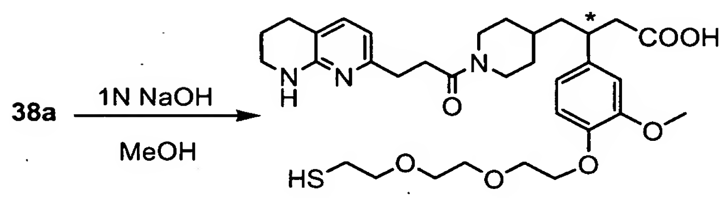


Compound **37a** (7.7 g, 41.2 mmol) was added to a solution of Compound **35a** (2.0 g, 4.0 mmol) and 1.0M potassium t-butoxide/ propanol in dry THF (13.0 mL, 13 mmol). The mixture was heated at 70 °C for 2 h, at which time the reaction mixture was diluted with brine (100 mL), and then extracted with diethyl ether (2 x 100 mL) and DCM (2 x 50 mL). The combined organic layers were dried over sodium sulfate, evaporated, and the resultant residue was purified by flash column chromatography (silica gel, 4 x 16 cm). The column was eluted with DCM (500 mL), followed by DCM/ 10% NH_4OH (0.1 % aq) in MeOH: 98/2 (0.5L), 95/5 (1L), and 90/10 (1L). The fractions were concentrated to give 1.11 g of Compound **37b**: LRMS: 645.32 m/z; ^1H NMR ($CDCl_3$) δ: 7.1 (d, 1H), 6.9 (d, 1H), 6.7 (d, 1H), 6.7 (s, 1H), 6.4 (d 1H), 4.7 (broad s, 1H), 4.55 (t, 1H), 4.2 (t, 2H), 3.9 (t, 2H), 3.85 (s, 3H), 3.8-3.7 (m, 6H), 3.65 (t, 2H), 3.6 (s, 3H) 3.4 (m, 2H), 3.1 (m, 1H), 2.85 (q, 2H), 2.7 (m, 3H), 2.5 (d, 2H), 2.4 (m, 1H)1.9 (m, 2H), 1.8 (m, 1H), 1.6-1.4 (m, 3H), 1.3 (m, 1H) and 1.0 ppm (m, 2H).

Example 38



38a



38b

Potassium thioacetate (1.94 g, 17.0 mmol) was added to a solution of Compound **37b** (1.1 g, 1.7 mmol) in dry DMF (11 mL). The reaction was complete after 1.5 h of stirring at 70 °C. The mixture was to cooled, diluted with water (300 mL), and the mixture was extracted with EtOAc (3 x 100 mL). The organic phase was washed with brine (5 x 100 mL), dried over sodium sulfate, evaporated, and the resultant residue was purified by flash chromatography (silica gel, 4 x 20 cm), eluting first with pure EtOAc (500 mL), then pure DCM (500 mL), followed by DCM/ 10% NH_4OH (0.1 % aq) in MeOH: 98/ 2 (1L), 95/ 5 (1L) and 90/ 10 (1L). Upon concentration of the fractions, Compound **38a** was isolated (1.07 g) as a yellow oil.

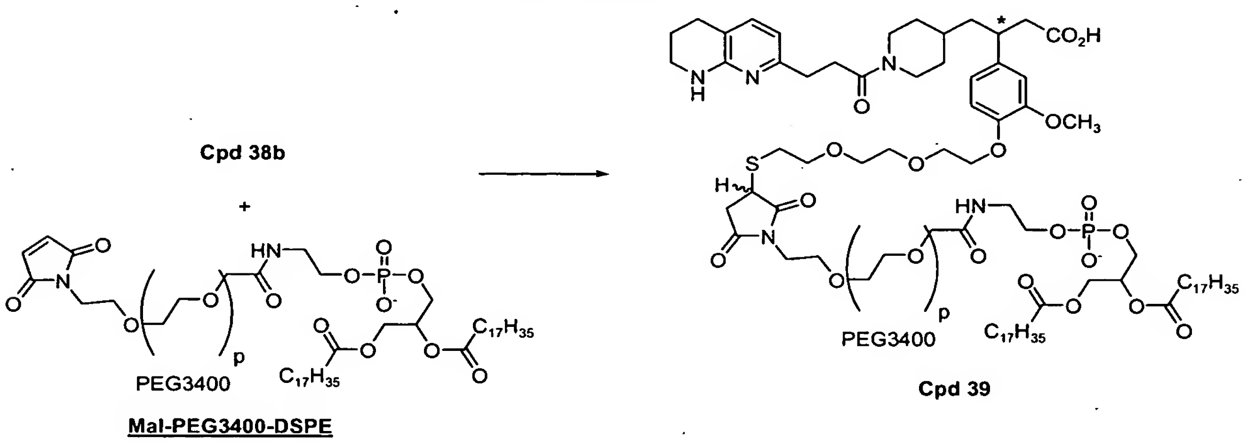
Compound **38a** (1.0 g, 1.5 mmol) was treated with of 3N NaOH (1.46 mL, 4.37 mmol) in MeOH (4.4 mL). After 21 h of stirring at ambient temperature, 2N HCl (approx. 1.0 mL) was added to achieve pH 7. The reaction mixture was transferred into a test tube, using MeOH for rinsing, and purified by several separate HPLC runs (12 min per run, 35 mL/ min), eluting with a gradient of 25-45% CH_3CN: H_2O/ 0.1 % TFA on a C18 reverse phase column (100 x 30 mm). Upon lyophilization, Compound **38b**

was obtained as a white powder: LRMS: 629.31 m/z; ^{1}H NMR ($CDCl_3$) □9.8 (br s, 1H), 7.3 (d, 1H), 6.95 (br s, 2H), 6.8 (d, 1H), 6.7 (d, 1H), 6.7 (s, 1H), 6.4 (d, 1H), 4.5 (t, 1H), 4.0-3.8 (m, 3H), 3.8 (s, 3H), 3.7 (m, 2H), 3.7-3.6 (m, 6H), 3.5 (m, 2H), 3.1 (m, 1H), 3.0 (m, 3H), 2.8-2.6 (m, 4H), 2.1 (d, 2H), 2.5 (t, 1H), 2.0-1.8 (m, 3H), 1.6 (t, 2H), 1.5 (m, 1H), 1.3 (m, 1H), and 1.0 ppm (m, 2H).

Compound **12b** was tested in the $\alpha_V\beta_3$ and $\alpha_V\beta_5$ binding assays described in Biological Example 4 with the following results:

ASSAY	RESULT FOR **Cpd 12b**
$\alpha_V\beta_3$ Binding Affinity	IC_{50} = 1.8 nM
$\alpha_V\beta_5$ Binding Affinity	IC_{50} = 9.6 nM

Example 39



Compound 39 was characterized by high pressure liquid chromatography (HPLC) using the conditions summarized in Table 1. The results are shown in Figs. 1A-1B, where Fig. 1A shows the HPLC chromatogram for a Mal-PEG-DSPE (PEG molecular weight 3400 Daltons) before conjugation to Cpd **38b**. The Mal-PEG-DSPE compound yields three peaks, one each at 20.42 minutes, which represents 78% of the total, at 23.73 minutes and 23.90 minutes, which together are about 22% of the total. Fig. 1B shows the Mal-PEG-DSPE compound after reaction with Cpd **38b**, to yield Cpd **39**. Conjugation of Mal-

PEG-DSPE resulted in the peak at 20.42 minutes to shift to conjugate peaks of 19.02 minutes and 19.82 minutes. The Mal-PEG-DPSE peaks at 23.73 minutes and 23.90 minutes shifted to conjugate peaks at 22.13 minutes and 22.78 minutes. The peaks at 23.42 minutes and 23.90 minutes are non-reacted Mal-PEG-DPSE (about 1.85% percent of the total). The peak at 19.02 minutes represents about 5% of the total conjugate, and the peak at 19.82 minutes represents about 73% of the total conjugate, while the peaks at 22.13 minutes and 22.78 minutes represent about 20% of the total conjugate.

Table 1. HPLC conditions.

mobile phase	100% = MeOH:THF:0.17M NH4Ac, 94:5:1
	20% = H2O:MeOH:THF:0.17M NH_4Ac, 79:19:1:1
column	Waters C-18, 5micron, 15.0 x 0.46 cm
oven	35^0 C
run time	12.5 min
flow rate	1 mL/min
detection	UV 216, 340 nm
% grad.	50% - 100%

Example 40

Liposomes comprised of hydrogenated soy phosphatidylcholine, cholesterol, and methoxy-poly(ethylene glycol)-distearolyphosphatidylethanolamine (HSPE:Chol:mPEG-DSPE, 56.4:38.3:53 molar ratio, mPEG molecular weight 2000 Daltons) and containing entrapped doxorubicin (Doxil®/Caelyx®) were prepared as described in the art (see, for example, U.S. Patent No. 5,103,556; 5,213,804).

Micellar solutions of the targeting conjugate identified as Formula (Ia) or Formula (1b) were prepared by hydrating a dried lipid film of the conjugate with buffer to yield a solution of ligand conjugates at varying concentrations.

The transfer of the lipid-polymer-ligand conjugate into the pre-formed Doxil® liposomes was initiated by mixing a 60 μL aliquot of a micellar solution of the targeting conjugates to provide 2.756 μg, 5.513 μg, and 11.026 μg of the ligand conjugate with 1 mL of the pre-formed liposomes. The mixtures were incubated at 60 ^{0}C for 1 hour.

Analysis showed the ratios of ligand/liposome were 18, 36, and 72 for the ligand conjugate/liposome solutions having ligand conjugate amounts of 2.756 μg, 5.513 μg, and 11.026 μg, respectively. The insertion efficiency of each was determined to be 100%, 87.41%, and 87.96% in each solution, respectively.

Biological Experimental Examples

As demonstrated by biological studies described hereinafter, as shown in Table I, the compounds of the present invention are αvβ3 and αvβ5 integrin receptor antagonists useful in treating an integrin mediated disorder.

Example 1

In Vitro Solid Phase Purified αvβ3 Binding Assay

The vitronectin/αvβ3 binding assay methods were derived from Mehta et al. (*Biochem J*,. **1998**, *330*, 861). Human $\alpha_v\beta_3$ (Chemicon International Inc., Temecula, CA), at a concentration of 1 μg/ml dissolved in Tris buffer (20 mM Tris, 1 mM $CaCl_2$, 1 mM $MgCl_2$, 10 μM $MnCl_2$, 150 mM NaCl), was immobilized on Immulon 96 well plates (Dynex Technologies, Chantilly, VA) overnight at 4 °C. Plates were washed and treated with blocking buffer (3 % BSA in Tris buffer) for 2 h at 37 °C. Plates were then rinsed 2 times with assay buffer comprised of Tris buffer. Synthesized compounds were added to wells in duplicate immediately prior to the addition of 2 nM vitronectin (Sigma, St. Louis, MO). Following a 3 hour incubation at 37 °C, plates were washed 5 times in assay buffer. An anti-human vitronectin IgG rabbit polyclonal antibody (Calbiochem, San Diego, CA) was added (1:2000) and plates were incubated for 1 hour

at room temperature. VectaStain ABC peroxidase kit reagents (Vector Laboratories, Burlingame, CA) employing a biotin labeled anti-rabbit IgG, were utilized for detection of bound antibody. Plates were read at 490 nm on a Molecular Devices (Sunnyvale, CA) microplate reader. Table 1 shows the results of the in vitro solid phase purified αvβ3 binding assay for representative compounds of the present invention.

Example 2

In Vitro Solid Phase Purified GP IIb/IIIa Binding Assay

A 96 well Immulon-2 microtiter plate (Dynatech-Immulon) was coated with 50 μL/well of RGD-affinity purified GP IIb/IIIa (effective range 0.5-10 μg/mL) in 10 mM HEPES, 150 mM NaCl, 1 mM $MgCl_2$ at pH 7.4. The plate was covered and incubated overnight at 4 °C. The GP IIb/IIIa solution was discarded and 150 μL of 5% BSA was added and incubated at RT for 1-3 h. The plate was washed extensively with modified Tyrodes buffer. Biotinylated fibrinogen (25 μL/well) at 2 x final concentration was added to the wells that contain the test compounds (25 μL/well). The plate was covered and incubated at RT for 2-4 h. Twenty minutes prior to incubation completion, one drop of Reagent A (VectaStain ABC Horseradish Peroxidase kit, Vector Laboratories, Inc.) and one drop Reagent B were added with mixing to 5 mL modified Tyrodes buffer mix and let stand. The ligand solution was discarded and the plate washed (5 x 200 μL/well) with modified Tyrodes buffer. Vecta Stain HRP-Biotin-Avidin reagent (50 μL/well, as prepared above) was added and incubated at RT for 15 min. The Vecta Stain solution was discarded and the wells washed (5 x 200 μL/well) with modified Tyrodes buffer. Developing buffer (10 mL of 50 mM citrate/phosphate buffer @ pH 5.3, 6 mg *o*-phenylenediamine, 6 μL 30% H_2O_2; 50 μL/well) was added and incubated at RT for 3-5 min and then 2 N H_2SO_4 (50 μL/well) was added. The absorbance was read at 490 nM. Table 1 shows the results of the in-vitro solid phase purified GP IIb/IIIa binding assay for representative compounds of the present invention.

Example 3

In Vitro Solid Phase Purified αvβ5 Binding Assay

The vitronectin/$\alpha_V\beta_5$ binding assay method was performed in the same manner as the vitronectin/$\alpha_V\beta_3$ binding assay of Example 2, with the difference that 1 μg/mL of

human purified $\alpha_V\beta_5$ (Chemicon International, Inc.) was immobilized onto Immulon 96 well plates (Dynex Technologies) instead of $\alpha_V\beta_3$. All other aspects of the assay including buffers, reagents and incubation times remain unchanged.

Table 1

Cpd	$\alpha_v\beta_3$IC$_{50}$ (uM)		$\alpha_v\beta_5$ IC$_{50}$ (uM)		$\alpha_{IIb}\beta_3$ IC$_{50}$ (uM)	
1	0.0560 ± 0.007	N=2	>5	ND	4.33 ± 0.15	N=2
2	5.4000 ±	N=1			4.78 ± 1.013	N=2
3	0.0036 ± 0.0004	N=5	2.5		0.21	N=1
4	0.0005 ± 0.0001	N=3	0.0355 ± 0.0089	N=4	0.87 ± 0.19	N=2
5	0.0037 ± 0.0014	N=3	0.2607 ± 0.0569	N=3	14.84 ± 0.68	N=2
5-3	0.1613	N=1	>5	N=1	ND	
5-4	0.0054 ± 0.0002	N=3	0.1616 ± 0.0627	N=3	9.82	N=1
6	0.0076 ± 0.0021	N=2	0.54	N=1	1.62 ± 0.05	N=2
7	0.0082 ± 0.0014	N=2	0.0395 ± 0.0085	N=2	1.67 ± 0.74	N=2
8	0.0179 ± 0.0034	N=4	0.253	N=1	1.36 ± 0.43	N=2
9	>1	N=1	ND		8.51 ± 2.36	N=2
10	0.0024 ± 0.0013	N=2	0.0335 ± 0.0075	N=2	1.67	N=1
11	0.0011 ± 0.0002	N=3	0.0023 ± 0.0009	N=3	2.52 ± 0.30	N=2
12	0.0042 ± 0.0014	N=3	0.078 ± 0.017	N=2	0.136± 0.003	N=2
13	0.0032 ± 0.0006	N=2	0.036 ± 0.0133	N=2	11.09 ± 3.40	N=2
14	0.0361 ± 0.0001	N=2	0.108 ± 0.034	N=1	5.04	N=1
15	0.0019 ± 0.0002	N=4	0.0334 ± 0.0063	N=4	4.03 ± 0.43	N=2
16	0.2810	N=1	0.775	N=1	25.38	N=1
17	0.0008 ± 0.0001	N=4	0.0313 ± 0.0060	N=4	6.60 ± 1.42	N=2

Table 1

Cpd	$\alpha_v\beta_3 IC_{50}$ (uM)		$\alpha_v\beta_5$ IC_{50} (uM)		$\alpha_{IIb}\beta_3$ IC_{50} (uM)	
18	>5	N=1	>5	N=1	>50	N=1
19	0.0025 ± 0.0004	N=3	0.0171 ± 0.0025	N=3	13.77 ± 9.69	N=2
19-1	0.0367	N=1	1.12	N=1	>50	N=1
19-2	0.0013 ± 0.0001	N=2	0.0092 ± 0.0004	N=2	12.9	N=1
19-3	0.0447 ± 0.0204	N=2	1.17 ± 0.02	N=2	ND	
19-4	0.0013 ± 0.0007	N=3	0.0075 ± 0.0018	N=3	4.86	N=1
20	0.1417 ± 0.027	N=3	0.995	N=1	1.80	N=1
21	0.0280 ± 0.0031	N=3	0.78	N=1	1.80 ± 0.63	N=2
21b	0.405	N=1	0.28	N=1	1.97	N=1
21a	0.0213 ± 0.0019	N=3	0.8413 ± 0.4054	N=3	5.31	N=1
22	0.0046 ± 0.0008	N=3	0.195	N=1	0.43 ± 0.07	N=2
23	0.2980 ± 0.1460	N=2	2.010	N=1	4.93	N=1
24	0.3070	N=1	0.387	N=1	19.30	N=1
25	0.0456 ± 0.0066	N=2	0.773 ± 0.118	N=2	8.67 ± 1.72	N=2
26	0.0277 ± 0.0053	N=2	0.5	N=1	5.92	N=1
27	0.0480	N=1	0.81	N=1	1.62 ± 0.56	N=2
28	0.0007 ± 0.0002	N=3	0.0027 ± 0.0008	N=4	6.10 ± 2.44	N=2
28a	0.0003 ± 0.0002	N=2	0.0042 ± 0.0018	N=2	1.83 ± 0.57	N=2
28b	0.0208 ± 0.0053	N=2	0.1262 ± 0.0448	N=2	24.26	N=1
29	0.0022 ± 0.0008	N=3	0.119 ± 0.0150	N=3	1.74 ± 0.89	N=2
30	0.0010 ± 0.0002	N=3	0.0028 ± 0.0001	N=3	14.39 ± 5.98	N=2
30a	0.0004 ± 0.0002	N=3	0.0019 ± 0.0004	N=3	2.93 ± 1.86	N=2

Table 1

Cpd	$\alpha_v\beta_3 IC_{50}$ (uM)		$\alpha_v\beta_5$ IC_{50} (uM)		$\alpha_{IIb}\beta_3$ IC_{50} (uM)	
30b	0.0317 ± 0.0147	N=2	0.0482 ± 0.0028	N=2	>50	N=1
31	0.0330	N=1	0.3	N=1	21.57 ± 4.87	N=2
32	0.0008 ± 0.0002	N=3	0.0022 ± 0.0007	N=3	1.055 ± 0.56	N=2
33	0.0013 ± 0.0004	N=3	0.0226 ± 0.0052	N=3	>50	N=1
34	0.1476 ± 0.1004	N=2	1.041 ± 0.109	N=2	>50	N=1
35	0.0007 ± 0.0004	N=2	0.0007 ± 0.0002	N=3	0.965 ± 0.07	N=2
36	0.0008 ± 0.00006	N=4	0.0007 ± 0.0002	N=3	3.11 ± 0.04	N=2
36a	0.0004	N=3	0.0009 ± 0.0006	N=2	0.79 ± 0.05	N=3
36b	0.084	N=1	0.129	N=1	>50	N=1
37	0.0158 ± 0.0043	N=2	0.0897 ± 0.0116	N=3	>50	N=1
38	0.4840	N=1	2.11	N=1	>50	N=1
39	0.0066 ± 0.0018	N=2	0.0287 ± 0.0133	N=2	>50	N=1
40	0.0052 ± 0.0002	N=2	0.308 ± 0.0630	N=2	23.95 ± 9.89	N=2
41	0.0018 ± 0.0010	N=2	0.8725 ± 0.1575	N=2	19.3 ± 2.60	N=2
42	0.0007 ± 0.0003	N=3	0.0189 ± 0.0046	N=3	5 ± 0.74	N=2
43	0.0079 ± 0.0007	N=2	0.2225 ± 0.0885	N=2	28.82 ± 15.8	N=2
44	0.0022 ± 0.0009	N=3	0.002 ± 0.0006	N=3	5.44 ± 1.1	N=2
45	0.0008 ± 0.0001	N=3	0.0017 ± 0.0003	N=3	6.61 ± 2.85	N=2
46	0.0035 ± 0.0006	N=2	0.0659 ± 0.0171	N=2	13.64 ± 1.33	N=2
47	0.0014 ± 0.0007	N=3	0.0046 ± 0.0017	N=3	1.47 ± 0.37	N=2
48	0.0010 ± 0.0005	N=3	0.0033 ± 0.0014	N=3	1.21 ± 0.20	N=2
49	0.0018 ± 0.0005	N=3	0.0895 ± 0.0255	N=2	0.16 ± 0.02	N=3

Table 1

Cpd	$\alpha_v\beta_3$IC$_{50}$ (uM)		$\alpha_v\beta_5$ IC$_{50}$ (uM)		$\alpha_{IIb}\beta_3$ IC$_{50}$ (uM)	
50	0.0156 ± 0.0044	N=4	0.676	N=1	0.19 ± 0.04	N=2
51	0.0030 ± 0.0006	N=4	0.169 ± 0.019	N=2	0.48 ± 0.01	N=2
52	0.0064 ± 0.0014	N=4	>50	N=1	0.57 ± 0.04	N=2
53	0.0298 ± 0.0137	N=5	0.1375 ± 0.0415	N=2	0.94 ± 0.05	N=2
54	0.0017 ± 0.0005	N=3	0.0347 ± 0.0117	N=3	0.24	N=1
55	0.0950	N=1	0.737	N=1	15.59	N=1
56	0.0019 ± 0.0006	N=3	0.0245 ± 0.0065	N=2	39.12 ± 0.785	N=2
56a	0.0005 ± 0.0002	N=3	0.0265 ± 0.0034	N=3	14.66	N=1
56b	0.3263 ± 0.0894	N=3	0.8096 ± 0.1045	N=3	ND	
57	0.0016 ± 0.0007	N=3	0.0109 ± 0.0042	N=3	3.04 ± 0.55	N=2
58a	0.0004± 0.0003	N=3	0.0323 ± 0.0082	N=3	1.44 ± 0.39	N=2
58b	0.083 ± 0.020	N=2	0.5760 ± 0.1490	N=2	35.5	N=1
59	0.0026 ± 0.0014	N=2	0.0096 ± 0.0038	N=2	7.805 ± 4.67	N=2
60	0.0010 ± 0.0008	N=2	0.0309 ± 0.0006	N=2	4.53 ± 2.47	N=2
61	0.0045 ± 0.0007	N=3	0.0253 ± 0.0073	N=3	37.45± 31.58	N=2
62	0.0900 ± 0.0020	N=2	0.1700 ± 0.0810	N=2	>50	N=1
63	0.0018 ± 0.0008	N=3	0.0070 ± 0.0008	N=3	10.23 ± 6.41	N=2
64	0.0615 ± 0.0055	N=2	0.1473 ± 0.0847	N=2	>50	N=1
65	0.0008	N=2	0.0346 ± 0.0002	N=2	3.84	N=1
66	0.0012 ± 0.0001	N=3	0.0103 ± 0.0014	N=3	28.27	N=1
67	0.048 ± 0.0030	N=2	0.176 ± 0.0350	N=2	7.82	N=1
68	0.413	N=1	>1	N=1	35.6	N=1

Table 1

Cpd	$\alpha_v\beta_3 IC_{50}$ (uM)		$\alpha_v\beta_5$ IC_{50} (uM)		$\alpha_{IIb}\beta_3$ IC_{50} (uM)	
69	>0.5	N=1	>1	N=1	>50	N=1
70	>0.5	N=1	>1	N=1	>50	N=1
71	>0.5	N=1	>1	N=1	>50	N=1
72	>0.5	N=1	>1	N=1	>50	N=1
73	>0.5	N=1	>1	N=1	>50	N=1
74	0.193	N=1	>1	N=1	>50	N=1
75	0.0053 ± 0.0010	N=2	0.0419 ± 0.0052	N=3	>50	N=1
76	0.0018 ± 0.0003	N=2	0.0397 ± 0.0121	N=2	5.38	N=1
76a	0.0011± 0.0002	N=2	0.0169± 0.0021	N=2	10.38	N=1
77	0.138	N=1	0.789 ± 0.065	N=2	ND	
78	0.0057 ± 0.0001	N=2	0.0260 ± 0.0030	N=2	24.72	N=1
79	0.0035 ± 0.0015	N=3	0.025 ± 0.0060	N=2	40.23	N=1
81	0.0067 ± 0.0002	N=3	0.0101 ± 0.0017	N=3	22.73	N=1

While the foregoing specification teaches the principles of the present invention, with examples provided for the purpose of illustration, it will be understood that the practice of the invention encompasses all of the usual variations, adaptations and/or modifications as come within the scope of the following claims and their equivalents.

Example 4

Targeting Ligand and TargetingConjugate Binding Assay

The ability of compounds to inhibit binding of $\alpha_v\beta_3$ or $\alpha_v\beta_5$ to vitronectin was measured as previously described in Luci, D. K.; Santulli, R. J.; Gauthier, D. A.; Ghosh, S.; Kinney, W. A.; DeCorte, B.; Galemmo, R. A. Jr.; Lewis, J. M.; Proost, J. C.;

Tounge, B. A.; Dorsch, W. E.; Wagaman, M. W.; Damiano, B. P.; Maryanoff, B. E. *Heterocycles* **2004**, *62*, 543-557. Human $\alpha_v\beta_3$ or $\alpha_v\beta_5$ (Chemicon International Inc.) dissolved in Tris buffer (20 mM Tris, 1 mM $CaCl_2$, 1 mM $MgCl_2$, 10 μM $MnCl_2$, 150 mM NaCl) was immobilized (1 μg/ mL) on Immulon 96 well plates (Dynex Technologies) overnight at 4 °C. Plates were blocked with 3% BSA in Tris buffer for 2 h at 37 °C. Plates were then rinsed 2X in assay buffer (Tris buffer with 0.3% BSA and 0.2% Tween-20). Five minutes prior to the addition of 4 nM vitronectin (Sigma Chemical Co.), compounds were added to wells in duplicate. Following 3 h at 37 °C, plates were washed 5X in assay buffer. An anti-human vitronectin IgG rabbit polyclonal antibody (Calbiochem Inc.) was added (1:2000) and plates were incubated for 1 h at room temperature. VectaStain ABC peroxidase kit reagents (Vector Laboratories) employing a biotin labeled anti-rabbit IgG, were utilized for detection of bound antibody (490 nm).

Adhesion of endothelial cells to vitronectin is both $\alpha_V\beta_3$ and $\alpha_V\beta_5$ mediated. The ability of the liposome conjugates to inhibit human microvascular endothelial cell (HMVEC) adhesion to vitronectin was evaluated. Cytomatrix cell adhesion strips coated with vitronectin (Chemicon) were rehydrated with 200 μl of PBS for at least 15 minutes at room temperature and then aspirated. HMVECs (Clonetics) were trypsinized to disperse cells from culture flask and dissolved in DPBS with 0.1 % BSA (assay buffer). Cells were fluorescently labeled with 5 μM Calcein AM (Molecular Probes) and incubated in the dark for 30 min @ 37 °C. After incubation, cells were washed 2X in assay buffer and cell number adjusted to 1 X 10^6/ mL. A 50 μL sample of compound was added to each well followed by 50 μL of the cell suspension. Plates are incubated for 1 h @ 37 °C, 5 % CO_2. After 1 h, plates were washed gently with warm assay buffer and adherent cells lysed for 15 min in 100 μL of 1 M Tris pH 8.0 with 1 % SDS. Fluorescent Intensity was determined using a Cytoflluor 2300 plate reader (Applied Biosytems) set at 485 excitation and 530 emission.

HT-29 colon carcinoma cells adhere to fibronectin via the integrin $\alpha_V\beta_6$ as described in Kraft, S.; Diefenbach, B.; Mehta, R.; Jonczyk, A; Luckenbach, G.A.; Goodman, S.L. *J. Biol. Chem.* **1999**, 274, 1979-1985. To determine if the liposome-

conjugated can inhibit this interaction the following adhesion assay was utilized. The ability of compounds to block adhesion of HT-29 cells was carried out in a similar fashion to the HMVEC/vitronectin assay described above. The only differences in protocol were that 1) Cytomatrix cell adhesion strips coated with fibronectin (Chemicon) were utilized and 2) HT-29 cells (ATCC) were the cell used in all experiments (same density, same labeling procedure).

Prospective Example 5

Young (4-6 week) female severe combined immune deficient (SCID) mice are injected with a tumor cell line expressing $\alpha5\beta3$ integrin receptors in the subcutaneous tissue of the flank or of the mammary fat pad. When palpable tumors achieve a size of about 300 mm3 (typically 14 days post inoculation), therapeutic, target-cell sensitized liposomes prepared as described in Example 40 and additionally inclucing a suitable label are administered by a single intravenous injection via the tail vein, in a volume of approximately 200 µL contining approximately 1 µmole total lipid. Animals are sacrificed at designated times post-injection, organs perfused with saline in situ, and tissues excised for analysis. Biodistribution of the liposomes is determined via detection of the liposome label or by quantitative localization of doxorubicin delivered by the liposomes.